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**The effectiveness of
multilevel botulinum toxin type A and
comprehensive rehabilitation
in children with cerebral palsy**

The studies presented in this thesis were carried out at the department of Rehabilitation Medicine of the VU University Medical Center Amsterdam, the department of Rehabilitation of the University Medical Center St. Radboud Nijmegen, the Center for Rehabilitation of the University Medical Center Groningen, the Rehabilitation Foundation Limburg (Franciscusoord) Valkenburg, the Department of Child Neurology, University Hospital Maastricht, and at the mytyschool de Regenboog in Haarlem, the Netherlands. The studies were part of the research programme Musculoskeletal Disorders of the Institute for Research in Extramural Medicine (EMGO).

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VRIJE UNIVERSITEIT

The effectiveness of
multilevel botulinum toxin type A and
comprehensive rehabilitation
in children with cerebral palsy

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
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Vanessa Antoinet Bernice Scholtes

geboren te Den Haag

promotor: prof.dr. J.G. Becher
copromotor: dr. A.J. Dallmeijer

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Chapter 1

Introduction and outline of the thesis

Cerebral Palsy

Cerebral palsy (CP) is a term used to describe a clinical syndrome, characterised by a persistent movement or posture disorder that results from a non-progressive disorder of the immature brain¹. CP is the most common motor disability in childhood, with an incidence of 1.5 - 3.0 per 1000 live births in western countries². For the population of the Netherlands, the prevalence in 1986-1988 was estimated at 2.4 per 1000 live births³.

Classification

Although the diagnosis of CP suggests an entity, it is a heterogeneous condition in terms of the type of movement disorder and the severity of impaired muscle functions⁴.

Type of movement disorder: CP can be classified according to the type of movement disorder into three groups: spastic paresis, dyskinetic paresis and ataxic paresis, but mixed movement disorders are also common. Classification, as such, is useful because for each group there is a different prognosis, and different methods of medical treatment are used for each group⁵.

The spastic paresis is the most common movement disorder (85%)^{2,6}. This is defined as a posture and movement-dependent tone-regulation disorder⁷. The most important clinical symptom of a spastic paresis is the loss or absence of muscle tone in a lying position, and an increase in muscle tone in a sitting position, or when standing, walking or running, depending on the degree of involvement. Spastic paresis can further be classified as unilateral or bilateral, according to the body parts involved. The unilateral group is referred to as hemiplegia, in which one arm and one leg on the same side of the body are involved, and the bilateral group is referred to as diplegia (e.g. the primary involvement is in the legs) and quadriplegia (e.g. all four extremities are involved: the arms are just as severely, or more severely, involved as the legs, or more). Another way to classify children with CP is according to their severity of gross motor limitations, by means of the Gross

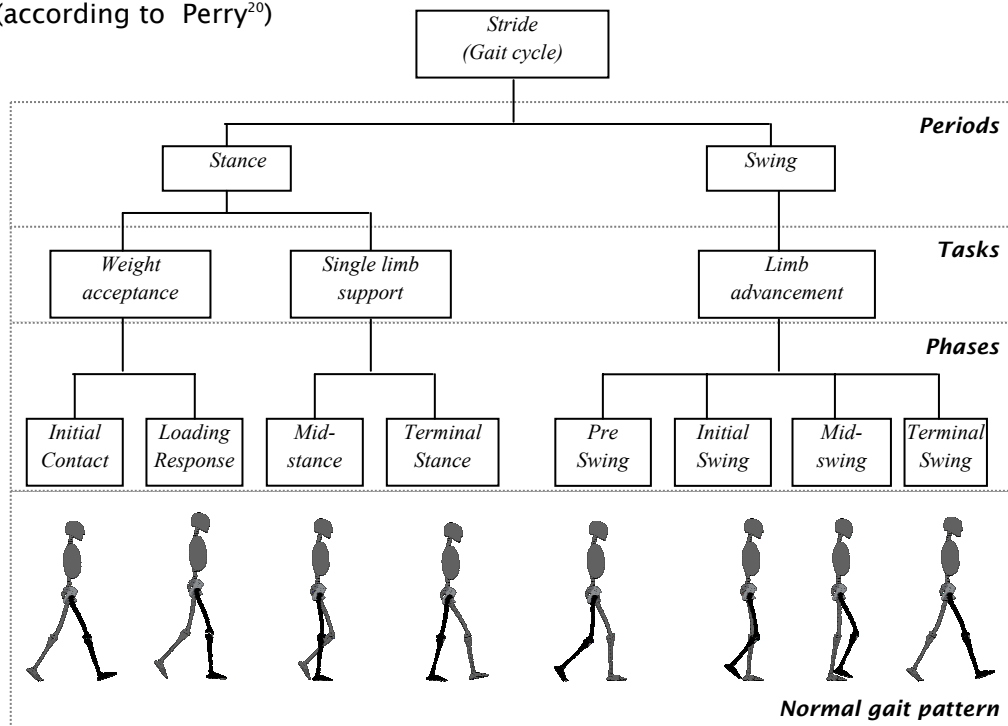
Motor Function Classification System (GMFCS)⁸. The GMFCS classifies children according to their functional abilities and their need for assistive technology and wheeled mobility. The GMFCS is a five-level system, based on age-specific criteria (age-range 0 - 12 years). From the age of 6, children with levels I and II walk without an assistive device, children with levels III and IV walk with an assistive device for respectively long or short distances, and children with level V are not able to walk. This thesis will focus on children with a hemiplegic and diplegic spastic paresis, with GMFCS levels from I to IV.

Impaired muscle functions: The impaired muscle functions that occur with spastic paresis are many, and secondary to a variety of neurological conditions resulting from the upper motor neuron syndrome that is inherent to the CP. They can be classified into two groups: (1) impairments of muscle activation, and (2) changes in biomechanical properties of muscles and connective tissues⁹. The impairments of muscle activation can be divided into a series of abnormal muscle activities or 'excess symptoms' (e.g. spasticity, hypertonia, hyperreflexia) and performance deficits caused by the reduction of voluntary muscle function, referred to as 'deficit symptoms' (e.g. paresis, loss of selective motor control).

Mobility and gait limitations

Impaired muscle functions lead to limitations in the activities of a child, which are experienced by the majority of children with CP^{10,11}. One of the most prominent activity limitations concerns mobility, described as movement by changing body position or location, or by transferring from one place to another¹². Mobility limitations are often related a deviated gait pattern, due to gait impairments. Many different gait patterns have been described in children with spastic paresis¹³. They are clinically classified according to the joint position(s) during a particular phase of gait (e.g. at the level of the ankle, the knee and/or the hip)^{7,14-17}.




Figure 1: The normal gait pattern in the different phases of the gait cycle (according to Perry²⁰)



Gait patterns which are characterised by knee flexion during the midstance phase of gait are thought to be particularly disturbing, since the natural course of development in these children is further deterioration in the flexion pattern¹⁸. This is generally accompanied by a deterioration in mobility¹⁹. This makes it important to identify these children at an early stage, and to start appropriate rehabilitation treatment in order to prevent deterioration in mobility by improving their gait pattern. Therefore, children with CP who walk with this so-called 'flexed knee gait'

are of special interest in the field of rehabilitation, and will be the focus of this thesis.

Figure 2: Different types of gait pattern of knee flexion during midstance, classified according to Rodda and Graham¹⁶ and the Amsterdam Gait Classification⁷

Classification of gait pattern according to:			
Joint position at anatomic levels	Illustration	Rodda and Graham	Amsterdam Gait Classification
Hip: flexed Knee: flexed Ankle: heel-rise, plantar flexion		Jump knee*	Type IV§
Hip: flexed Knee: flexed Ankle: heel-rise, neutral-dorsal flexion		Apparent equinus†	
Hip: flexed Knee: flexed Ankle: heel contact, dorsal flexion		Crouch gait‡	Type V§

*Jump knee = increased flexion at the hip and knee in early stance phase, through initial double support, with correction of the knee wave to normal or near normal extension in terminal stance, with increased plantar flexion at the ankle throughout the gait cycle²¹; †Apparent equinus = increased flexion at the hip and knee during stance and the ankle in neutral plantar / dorsal flexion (e.g. normal range)²²; ‡Crouch gait = increased flexion at the hip and knee and the ankle with increased dorsal flexion ('calcaneous') at the ankle²¹; §Minimal knee flexion >10°

Flexed knee gait

The flexed knee gait is specifically characterised by flexion of the knee ($> 10^\circ$) during midstance, with simultaneous flexion of the hip. The position of the ankle may vary from equinus (plantar flexion of the ankle and the foot) to dorsal flexion. The midstance is defined as the phase in the standing period during stride where there is only single limb support (Figure 1).

This phase starts when the contralateral leg is in initial swing, and ends when the contralateral leg passes the reference leg. Depending on the position of the ankle, the flexed knee gait can be classified as either type IV (knee flexion in midstance with heel-rise) or type V (knee flexion in midstance without heel-rise), according to the Amsterdam Gait Classification⁷ (Figure 2).

Other classifications of these gait patterns (see Rodda and Graham, 2001) are ‘jump knee’ or ‘apparent equinus’ for type IV, or ‘crouch gait’ for type V (Figure 2)¹⁶. The participants in the study described in this thesis were children with type IV and type V gait patterns.

Clinical assessment of spasticity

With respect to the cause of the flexed knee gait, it is postulated to be attributable to an underlying combination of decreased strength of the extensor muscles (i.e. glutei, quadriceps and/or tibialis posterior muscle), reduced length of the flexor muscles (i.e. psoas, hamstrings, gastrocnemius and/or soleus muscles)¹³ and/or abnormal involuntary muscle overactivity. With regard to the latter, spasticity (defined as ‘a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes [muscle tone] with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome’²³), is also considered to be causative. The presence of spasticity can be assessed during clinical examination. However, for many years

there has been an ongoing discussion with respect to the assessment of spasticity. In this thesis we will add to that discussion.

Of all the different methods to assess spasticity, clinical scales are the most frequently used in clinical practice²⁴. Spasticity is clinically characterised by a velocity-dependent increase in muscle tone, demonstrated at a certain angle in the range of motion (ROM) in response to passive muscle stretch. In order to demonstrate the velocity-dependency, the instrument should assess spasticity by applying both a slow and a fast stretch. In an extensive review, described in Chapter 2 of this thesis, we found that different clinical spasticity scales have been developed and used in the evaluation of CP. Unfortunately, most scales are of limited value as a measure of spasticity because they only use one, usually undefined, velocity of stretch. This makes them unsuitable to discriminate between spasticity and other symptoms of abnormal involuntary muscle overactivity which also lead to increased muscle tone, but which are typically non-velocity-dependent, such as hypertonia due to tonic stretch reflex (TSR) activity, or even hypertonia due to a change in biomechanical properties²⁵⁻²⁷. Each of these symptoms may require a different method of medical treatment. Therefore, when the aim is anti-spasticity treatment, assessment of the velocity-dependent character of spasticity seems crucial. A new clinical spasticity scale was therefore needed. This led to the development of the Spasticity Test, which will be presented in Chapter 3.

Treatment of flexed knee gait

As has already been explained, the flexed knee gait is thought to result from an underlying combination of different impairments. Due to the heterogeneity of CP, the presence and severity of spasticity and the other impaired muscle functions varies per patient. Nonetheless, what is characteristic for all patients with CP is that the impairments are not equally spread throughout their muscles. This results in a muscle imbalance, i.e. in an agonist-antagonist couple (such as flexor-

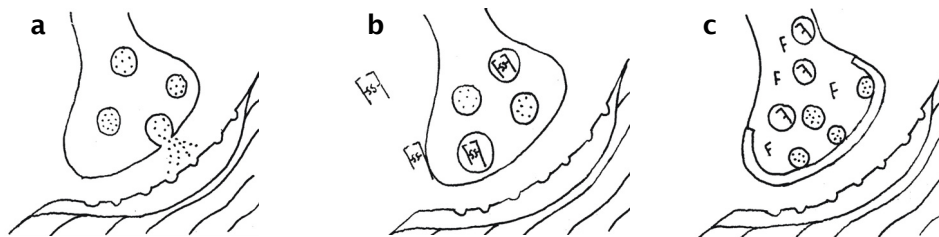
extensor) there is generally more spasticity and/or muscle shortening in one than in the other. Treatment of this muscle imbalance is considered to be the main prerequisite for potential improvement in mobility. The treatment rationale is therefore to aim at decreasing muscle activity in the spastic (usually flexor) muscles, stretching the shortened (usually flexor) muscles and strengthening the weakened (usually extensor) muscles, at the same time. To decrease spasticity, botulinum toxin type A (BTX-A) can be injected in the muscle, and a comprehensive rehabilitation treatment, consisting of intensive physical therapy, orthosis and serial casting, can be used to train the weaker extensor muscles, stretch the shorter flexor muscles and increase mobility training. Such treatment has been evaluated in this thesis, and for this purpose we performed a randomised controlled trial, the BOLIEN study, in which we evaluated the effect of multilevel BTX-A injections and comprehensive rehabilitation, compared to usual care (low-frequency physical therapy). Multilevel BTX-A treatment refers to the injection of multiple muscles (around the hip, knee and ankle) within one treatment session, which is particularly indicated in children with a gait which is characterised by flexion of the knee in midstance.

The effects of this intervention on the domain of body function and structure; e.g. spasticity, muscle length and gait pattern, has been described in Chapter 4. From the perspective of rehabilitation, it is particularly relevant to improve the mobility of children who walk with flexed knees. Establishing the effectiveness of this treatment on mobility, as part of the domain of activity, was therefore the main goal of the BOLIEN study, and this will be described in Chapter 5.

Botulinum toxin type A injections

The neurotoxin BTX-A is produced by the anaerobic bacterium *Clostridium Botulinum*. Injected in a muscle, BTX-A acts at the neuromuscular junction by blocking the release of acetylcholine²⁸ (Figure 3). The dose-dependent muscle-relaxation that is induced is temporal. After a period of 2 to 4 months, the muscle is re-innervated, first by nerve-sprouting and the formation of new synaptic contacts, and later by recovery of the originally affected nerve-endings²⁹.

Figure 3: Action of botulinum toxin type A (BTX-A)



a: normal innervation of a muscle: through fusion of the vesicle with the cell membrane, acetylcholine is released in the nerve terminal, which initiates muscle contraction;
b: after injection of BTX-A, the heavy chain of the toxin binds to high affinity receptors at the cholinergic presynaptic nerve terminals and the toxin-receptor complex is internalised by endocytosis;
c: the heavy and low chain are cleaved and the light chain is released in the cytoplasm. The light chain interacts with the SNAP25 protein in the nerve terminal to prevent fusion of acetylcholine vesicle with the cell membrane and thereby blocks its release.

The application of BTX-A as a therapeutic tool in the treatment of gait patterns has gained popularity in the treatment of spastic CP, and in particular for equines gait, which is typically characterised by excessive ankle plantar flexion during stance, and leads to gait-instability. When the equines is caused by spasticity of the gastrocnemius muscle, this muscle is the target for injection. Since the early 1990s, many studies have reported on the efficacy of this single-muscle injection treatment³⁰⁻³⁶.

So far, there have been no reports on effectiveness of this treatment in children with a flexed knee gait. The flexed knee gait is considered to be due to the presence of spasticity in several muscles, which act over different joints (e.g. knee, hip and/or ankle). Therefore, to improve this gait pattern, all these muscles should be injected with BTX-A. When this is done in one session, this is referred to as 'multilevel BTX-A injection'.

Comprehensive rehabilitation

As has already been mentioned, injection with BTX-A is rarely an isolated treatment, because it only acts on one component of the muscle imbalance: i.e. spasticity. Other components of the muscle imbalance, such as muscle paresis and muscle shortening, remain unaffected. Therefore, the total treatment plan should also aim to improve muscle length and muscle strength. This is achieved by means of a comprehensive rehabilitation approach, including a period of intensive physical therapy after the BTX-A injections, the prescription of an appropriate orthosis, and, if necessary, serial casting.

The aim of intensive physical therapy after multilevel BTX-A treatment is to improve the mobility of the child by increasing muscle length and muscle strength and training motor activities. This should be achieved by a variety of safe, effective and fun training methods. However, there are no scientific reports that define the optimal intensity or contents of such a physical therapy program. The contents of the program should be adapted to the individual child, and should involve a timely progression in intensity. A 1-hour training schedule two to three times per week is recommended, for maintaining and improving muscle strength and flexibility³⁷. Intensified physical therapy following after BTX-A is also recommended. To benefit from the muscle relaxation effect³⁸, exercises to stretch the agonist spastic muscles and to strengthen the antagonistic weakened muscles can be performed more easily, and new motor activities can be re-learned with the aim to improve

mobility. Subsequently it is important that the intensity is increased in the period during which the toxin is most active (e.g. three to six weeks post-injection).

Ankle-foot-orthoses (AFOs) are also prescribed for children with spastic CP to correct their gait pattern^{39,40}. There are different AFO configurations, and the type of AFO depends on what needs to be corrected. When gait is characterised by persistent flexion of the knee, AFOs could be prescribed to support full knee-extension in terminal stance and to block the third rocker (heel-rise to toe-off)⁴⁰. These are either rigid (does not allow ankle dorsiflexion) or hinged (allows some ankle dorsiflexion) with a stiffened carbon sole, floor-reaction orthoses (FRO), or stiffened carbon inlays.

Finally, serial casting is prescribed if the passive dorsiflexion range is restricted by shortening of the gastrocnemius muscle (i.e. does not exceed 0° dorsiflexion).

Note; It should be obvious that the formulation of a total treatment plan for a child with CP, including the target muscle identification for multilevel BTX-A injection, the focus of the physical therapy program, the type of AFO prescribed, and the need for serial casting, is directly related to the child's underlying muscle imbalance. This is identified by means of gait-analysis and clinical examination, and is therefore highly child specific. This means that, in the study described in this thesis, the treatment plan for every child was unique, even though they all walked with a flexed knee gait. To illustrate how each individual treatment plan was formulated, a clinical case presentation for one of the participants in the study is presented in Appendix I.

Purpose of the thesis

The primary aim of this thesis was to determine the effectiveness of multilevel BTX-A injections and comprehensive rehabilitation on the mobility of children with spastic CP who walk with flexed knees. The second aim was to develop a new instrument for the clinical assessment of spasticity.

Outline of the thesis

The first part of this thesis describes the clinical assessment of spasticity. Chapter 2 gives an overview of all the instruments that can be used for the clinical assessment of spasticity in children with CP. The compliance of each instrument with the concept of spasticity was evaluated, and this resulted in the identifications of a number of concerns regarding the use of these instruments for the evaluation of spasticity.

Chapter 3 presents a clinical spasticity scale, the Spasticity Test (SPAT). The assessment procedure, the feasibility for use in clinical practice, and the intra-rater and inter-rater reliability of the scale are described.

The second part of this thesis describes the efficacy of multilevel BTX-A injections and comprehensive rehabilitation in children with a spastic paresis, who walk with flexed knee gait. Chapter 4 presents the results of the randomised controlled trial of the effect of multilevel BTX-A and comprehensive rehabilitation on gait pattern, spasticity and muscle length in these children, and Chapter 5 describes the results with regard to mobility. Since the characteristics of patients with CP differ widely, it is likely that certain patients will benefit more from this treatment than others. Therefore, the predictors for a favourable outcome of multilevel BTX-A and comprehensive rehabilitation on mobility and gait pattern in these children are evaluated in Chapter 6.

The final part of this thesis, Chapter 7, is the general discussion.

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Appendix I: Clinical Case Presentation

Basic information about the child

Personal information

The patient is a small 4½ year old boy (115 cm, 18.5 kilos).

Educational situation

He attends a regular elementary school.

Medical diagnosis

He has a symmetric bilateral spastic paresis.

Medical history

The patient was born at 30 weeks after a normal pregnancy. Brain-computed tomography and Magnetic Resonance Imaging scans showed white-matter damage of immaturity in the periventricular area (periventricular leukomalacia). The patient has been treated with physical therapy since the age of 6 months and has worn orthosis since the age of 3 years. He has not received any other treatments.

Aids and adaptations

The patient wears ankle foot orthosis (AFOs) indoors and outdoors. He has a two-wheeled bicycle with additional side-wheels, but the parents put him in a buggy for longer-distances, and have recently applied for a hand-driven wheelchair.

Present situation of the child

Present needs

The patient was referred to one of the four hospitals participating in the study for clinical evaluation, in order to determine the appropriate AFOs configuration to improve his gait pattern. He has had increasing difficulty in the fitting of his Floor Reaction AFOs and increased daily tripping and falling, secondary to excessive ankle plantar flexion (equinus) and flexed knee gait. He has no pain in the knees or feet when walking.

Appendix I: Clinical Case Presentation - continued

Current abilities

Mobility

The patient is classified as level II according to the Gross Motor Function Classification System.

He walks indoors, and for balance, he uses walls and furniture. He attains a sitting position through a supine position and a standing position through a sitting position. He maintains stand for 1 to 3 seconds, but in stand he cannot lift one leg, even with assistance. He can crawl alternately. He maintains a high-knee position and can walk 10 steps with high knees. Assistance is needed when he wants to maintain a half-knee position or wants to attain stand through a half-knee position with either knee. Outdoors, he can walk for 30 minutes (with little assistance), but he cannot stop and turn from walking without assistance, so needs help when crossing the street. He is not able to run.

Personal care

The patient is able to dress and undress without any assistance, but he needs complete assistance with tying and untying his shoe-laces and AFOs.

Learning, communication, social emotional functioning

The patient has good cognition, good communication and good social emotional functioning.

Impairments

Passive range of motion (ROM)

The patient has 130° hip flexion in both hips, and has 60° of hip abduction with his hips flexed. His prone hip extension is 0° bilaterally. His internal rotation is 60° in his right

Appendix I: Clinical Case Presentation - continued

hip and 40° in his left hip, and his external rotation is 25° bilaterally. His popliteal angles are 70° bilaterally. He has a 10° flexion-contracture in both knees. Both his ankles dorsiflex to 0° with knee flexion and to -5° with his knees extended.

Muscle function

Spasticity, as shown by the occurrence of a clear catch in response to a fast passive stretch, is present in the adductor muscles at 20° and in the rectus femoris at 60° bilaterally, in the right and left hamstrings muscles at 100° and 80°, respectively, and in the right and left gastrocnemius/soleus muscles at 50° and 40°, respectively. He has good selective motor control in ankles, knees and hips bilaterally.

Gait analysis

Clinical observation

The patient stands and walks with a bilateral gait pattern type IV (hip and knee flexion, ankle plantar flexion in midstance) according to the Amsterdam Gait Classification. He has bilateral toe-landing on initial contact, fore-foot varus rotation during loading response, and severe equinus without heel contact during the total stance phase. The knee flexion during midstance is 25° in the right leg and 30° in the left leg. There is endorotation of the foot during both the stance and the swing phase. During swing there is reduced progress towards knee extension, and he walks with slight endorotation-abduction in terminal swing (left > right). The step-length is reduced bilaterally.

Dynamic electromyogram (EMG) recordings

There is continuous bilateral activity of the rectus femoris muscles in both swing and stance; the vastus lateralis muscles demonstrate excessive activity during stance; there is prolonged activity of the hamstrings muscles in stance; the gastrocnemius are active during midstance, but not in terminal stance; and the tibialis anterior are continuously active, with an increase of phasic activity in terminal swing and loading response.

Appendix I: Clinical Case Presentation - continued

Interpretation

Perry²⁰ and Gage¹³ have described five prerequisites for normal gait. We will use these prerequisites as a basis for our interpretation of the patient's needs and clinical problems, in order to recommend adequate treatment.

Prerequisites of normal gait:

- (1) Stability in the stance phase of gait
- (2) Clearance of the foot in the swing phase
- (3) Proper foot preposition in swing
- (4) An adequate step-length
- (5) Conservation of energy

According to these five prerequisites, the specific problems of this patient are:

- (1) a bilateral instable base of support in stance, due to equinovarus position of the feet caused by abnormal activity (spasticity) and shortening of the gastrocnemius muscles;
- (2) an insufficient clearance caused by insufficient bilateral knee flexion during initial swing, resulting from an early onset of stretch reflex activity (spasticity) of the rectus femoris muscles in initial swing, which is confirmed by EMG;
- (3) an improper foot preposition due to both incomplete bilateral knee extension and endorotation/adduction of the hips, as well as insufficient bilateral foot-lift in terminal swing, resulting in an equinovarus position of the foot, caused by shortening of the gastrocnemius and hamstrings muscles, and abnormal hamstrings activity (spasticity) in terminal swing;
- (4) an inadequate step-length, caused by the lack of knee propulsion towards extension of the swinging leg;

Appendix I: Clinical Case Presentation - continued

(5) an energy-consuming gait pattern, due to bilateral knee flexion in midstance, caused by abnormal activity and shortening of the gastrocnemius and hamstrings muscles, for which the prolonged vastus lateralis activity is compensating. There is also a bilateral lack of active toe-off in terminal stance, due to insufficient gastrocnemius power, which is confirmed by EMG.

Treatment plan

With respect to the five gait prerequisites and the patient's complaint of falling (mainly prerequisites no. 1, 2 and 3) and difficulty of AFO fitting, not only new orthosis, but also multilevel BTX-A injections and serial casting are indicated for this patient:

- (1) BTX-A injections in the gastrocnemius muscles to reduce the equinovarus, serial casting to improve gastrocnemius muscle lengths, and prescription of AFOs to improve the base of support;
- (2) BTX-A injections in the rectus femoris muscles to improve clearance in initial swing;
- (3) BTX-A injections in the gastrocnemius muscles to reduce the equinovarus, BTX-A injections in the medial hamstring muscles to reduce the endorotation/adduction in terminal swing, and prescription of AFOs to reduce the equinovarus in terminal swing;
- (4) BTX-A injections in the hamstrings muscles to improve the knee extension during midstance, prescription of AFOs to improve knee extension during terminal stance, and (see treatment recommendation for prerequisite 2 'clearance of the foot in swing phase');
- (5) BTX-A injections in the hamstrings muscles to improve the flexed knee gait pattern, BTX-A injections in the gastrocnemius* muscles to improve the flexed knee gait pattern, bilateral serial castings to improve gastrocnemius muscle lengths, and prescription of AFOs to improve knee extension during terminal stance.

** note that the gastrocnemius power is insufficient in terminal stance: to prevent this from getting worse, the gastrocnemius should be injected with a low dose.*

Appendix I: Clinical Case Presentation - continued

Treatment received

Multilevel BTX-A

Dosage and injected muscles: The maximum age-adjusted dose for injection is 25U * 18 kilos = 450U Botox®. The maximum dose is 108U (6U/kg) per large muscle group and 72U (4U/kg) per small muscle group. The total dose injected in this patient was 400U (hamstrings (2 legs x 6 injection sites x 15U) [gracilis (2x2x15U), semimembranosus (2x2x15U), semitendinosus (2x2x15U)], rectus femoris (2 legs x 2 injections sites x 25U), gastrocnemius medialis (2 legs x 2 injections sites x 15U), gastrocnemius lateralis (2 legs x 2 injections sites x 15U))

Orthosis

Bilateral, non-hinged, Floor Reaction AFOs.

Serial casting

Bilateral serial castings, applied two weeks after injections, until 0° ankle dorsiflexion is reached with knee extended.

Intensive physical therapy

The patient is treated with a 12-week standardised physical therapy protocol. This starts one week after the injections, with a varying frequency of 3 (weeks 1 to 3, and weeks 7 to 12) to 5 (weeks 4 to 6) times a week. The physical therapy has three main aims:

- (1) improve the length of the iliopsoas, hamstrings, gastrocnemius and soleus muscles by means of passive and active stretches, as well as daily stretching exercises performed at home.
- (2) improve the strength of the quadriceps, gluteus medius and gluteus maximus muscles. Insufficient strength in these muscles is indicated by the patient's difficulties with the half knee position and standing on one leg.
- (3) improve functional mobility and gait pattern. The patient has difficulty in maintaining stand, stop and turn with arms free. He will be trained in this, with subsequent focus on the gait pattern.

Chapter 2

Clinical assessment of spasticity in children with cerebral palsy: a critical review of available instruments

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Abstract

This study reviews the instruments used for the clinical assessment of spasticity in children with cerebral palsy, and evaluates their compliance with the concept of spasticity, defined as a velocity-dependent increase in muscle tone to passive stretch. Searches were performed in Medline, Embase, and Cinahl, including the keywords 'spasticity', 'child', and 'cerebral palsy', to identify articles in which a clinical method to measure spasticity was reported. Thirteen clinical spasticity assessment instruments were identified and evaluated using predetermined criteria. This review consists of reports on the standardization applied for assessment at different velocities, testing posture, and quantification of spasticity. Results show that most instruments do not comply with the concept of spasticity; standardization of assessment method is often lacking, and scoring systems of most instruments are ambiguous. Only the Tardieu Scale complies with the concept of spasticity, but this instrument has a comprehensive and time-consuming clinical scoring system.

Introduction

Cerebral palsy (CP) is defined as a clinical syndrome characterized by a persistent disorder of posture or movement due to a non-progressive disorder of the immature brain¹. The most common movement disorder in CP is a spastic paresis², defined as a posture and movement-dependent tone regulation disorder. The clinical manifestations of spastic paresis vary widely, depending on the various impairments of muscle function that can be distinguished. Clinical symptoms of impaired muscle function can either be related to an impairment of muscle activation, leading to both deficit (or negative) and excess (or positive) symptoms, or to a change in biomechanical properties of muscles and connective tissues (Table 1)³.

The functional abilities of the child with spastic paresis often deteriorate during development. It is generally postulated that spasticity, a prominent symptom in spastic paresis, is related to this decline. Therefore, anti-spasticity treatment⁵⁻⁷ plays an important role in treating the child with CP. However, many other symptoms, such as muscle paresis⁸ (Table 1), also interfere, but remain unaffected by these anti-spasticity treatments. Careful assessment of which symptoms of impaired motor function are functionally limiting the individual patient is, therefore, essential in selecting the appropriate treatment. Clinical assessment to distinguish spasticity from other symptoms is only possible if a clear and unambiguous definition is given. Many different definitions have been proposed⁹⁻¹¹.

The most commonly used definition of spasticity is probably that of Lance: 'a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome'⁹. In this definition the clinical symptom of spasticity is a velocity-dependent increase in muscle tone. Stretching a muscle at a sufficiently high velocity is essential to elicit a stretch reflex at a certain angle in the range of

Table 1: Summary of clinical symptoms of impaired muscle function in spastic paresis⁴

<i>Impairment of muscle activation</i>	
<i>Deficit symptoms (signs of reduction or loss of normal voluntary muscle activation)</i>	
Paresis	Inadequate force
Loss of selective motor control	Impaired ability to activate and control selective or isolated movements across specific joints
Loss of dexterity of movement	Impaired ability to coordinate temporal and spatial activation of many muscles
Enhanced fatigability	Inadequate sustained force
<i>Excess symptoms (signs of abnormal involuntary muscle activation)</i>	
<i>Passive movement</i>	
Hypertonia (TSR)	Non-velocity-dependent resistance to passive movement experienced by the examiner as increased muscle tone, caused by continuous muscle activation (Tonic Stretch Reflex activity)
Spasticity	Velocity-dependent resistance to passive movement experienced by the examiner as increased muscle tone, caused by an increase in stretch reflex activity
Clonus	Involuntary rhythmic muscle contraction
<i>Active movement</i>	
Mirror movements	Involuntary, simultaneous, contralateral movement of a muscle caused by voluntary movement of the same muscle on the ipsilateral side of the body
Associated abnormal postures	Involuntary abnormal muscle activity related to posture or the performance of any task
Co-contraction	Simultaneous involuntary contraction of the antagonist at voluntary contraction of the agonist
<i>Abnormal reflexes</i>	
Hyperreflexia of tendon jerks	Raised reaction to tendon tap, extension of the reflexogenic zone, spread of reflexes
Abnormal nociceptive flexion reflexes	Abnormal pathological reflexes to painful stimuli (i.e. Babinski reflex)
Abnormal musculocutaneous reflexes	Abnormal pathological reflexes to cutaneous stimuli (i.e. adductor reflex)

Table 1: Summary of clinical symptoms of impaired muscle function in spastic paresis⁴ – continued

<i>Changes in biomechanical properties of muscle and other connective tissues</i>	
Contractures	Fixed shortening of muscle and tendon, resulting in a reduced range of motion
Hypertonia	Non-velocity-dependent resistance to passive stretch experienced by examiner as increased muscle tone, caused by biomechanical changes within muscle itself

motion, and the faster the stretch, the earlier and stronger the reflex component of the increased muscle tone will be¹². Many studies have shown this stretch-related muscle activity, validating the velocity-dependency¹³⁻¹⁵.

To assess spasticity clinically (without the use of special devices) and to verify the velocity-dependency, the intensity of the muscle tone elicited at very slow and at rapid passive joint movement is compared and graded. However, spasticity can also be quantified by measuring the joint angle at which the increase in muscle tone is encountered in a fast stretch^{10,15} and comparing it with the joint angle in a slow passive range of motion (ROM). As the severity of spasticity increases, this increase in muscle tone reflex is elicited earlier in the ROM¹⁶. It can lead to a ‘catch’^{12,17} of the muscle, defined as the sudden appearance of increased muscle tone, which leads to an abrupt stop during the dynamic phase of movement in a joint, somewhere before the end of the ROM.

Of significant influence on the increase in muscle tone and the joint angle of appearance, although ignored in Lance’s definition⁹, are the testing posture and the initial length from which the muscle is stretched^{14,18-20}, as well as any sensory stimulation (e.g. laughing) during the assessment^{21,22}. Various clinical instruments are used to evaluate spasticity. However, it is not known whether these instruments assess spasticity in accordance with the velocity-dependency defined by Lance. As other factors can modulate both the presence and the intensity of spasticity, standardization of the test protocol is required. This review focuses on the different instruments used to assess spasticity in children with spastic CP in

the clinical setting, and their report on a standardized test protocol. Questions addressed in this review include: which instruments for the clinical assessment of spasticity are used in children with CP?; Is there standardization for the assessment at different velocities of passive joint movement and the testing posture of the patient?; How is spasticity quantified?

Method

Search strategy

A comprehensive computerized sensitive search of the electronic databases Medline (January 1980 to March 2004), Embase (January 1980 to March 2004), and Cinahl (January 1982 to March 2004) was performed by two reviewers (VS and AB). The search strategy included the terms 'spasticity', 'cerebral palsy', and 'child'. The references of retrieved articles were checked. All citations identified by this search were entered into a bibliographic management software programme, Reference Manager.

Selection

The titles and abstracts were screened by one reviewer (VS). References were included if: (1) they included children (younger than 18 years) with a diagnosis of CP; (2) a clinical assessment of spasticity was described; (3) they were published as a full report or an abstract; and (4) the language was English, German, French, or Dutch.

Data extraction

A data-extraction form was used to register: (1) patient characteristics; (2) the clinical spasticity instrument(s) used; (3) whether the test protocol reported on different velocities of testing and on the testing posture of the patient; and (4) the

method of quantification. Some references did not describe the test protocol of the spasticity assessment, but reference was made to the original (or another) publication concerning the applied instrument. In that case, the publication that was referred to was retrieved and from this, the relevant data were extracted.

Results

Included studies

The search strategy resulted in the retrieval of 937 citations from the electronic databases. Screening these citations on diagnosis and assessment of spasticity resulted in 193 studies, and reference tracking resulted in 18 additional studies. Thus, 211 references were identified, 119 of which fulfilled the inclusion criteria. The references that were included comprised 12 review or overview articles, 103 studies, and 4 case reports. In these 119 publications, 13 different clinical spasticity assessment instruments were used (Table 2), which form the basis for this review.

Clinical grading scales for either spasticity or muscle tone have primarily been used to assess spasticity. Measurements of other excess symptoms that are related to spasticity (clonus and reflexes) were also reported in some of the references as being an ‘assessment of spasticity’. Because these are not true spasticity measures, but other symptoms of impaired muscle activation (see Table 1) we did not include them in this review.

Available assessment instruments of clinical spasticity

All of the instruments used for the clinical assessment of spasticity could be categorized into three main groups, according to their assessment technique and quantification (Table 3). The first group is referred to as the ‘Ashworth-like scales’, after Ashworth²³, who first described the principle of muscle tone assessment by

scoring the resistance encountered in a specific muscle group by passively moving a limb at one (non-) specified velocity through its ROM on a 5-point scoring scale. This is the original Ashworth scale (AS)²³. The AS has three modifications, all sharing the same principle. The first modification was made by the addition of an intermediate score, making it a 6-point scale: the Modified Ashworth scale-Bohannon (MAS-B)²⁴. A second modification combined the AS²³ with the MAS-B²⁴, and added grading for the severity of spasticity: the Modified Ashworth scale-Peacock (MAS-P)²⁵. A third modification, the New York University Tone Scale (NYU)²⁶, combined the AS²³ with the ROM at a fast velocity stretch.

The second group is referred to as 'Tardieu-like scales', after Tardieu²⁷, who described the principle of spasticity assessment by joint-angle measurement at different velocities of muscle stretch. Derived assessments are the Tardieu Scale (TS)²⁸ with which spasticity is clinically assessed by passive movement of the joints at three specified velocities and the intensity and duration of the muscle reaction to stretch (X) is rated on a 5-point scale, with the joint-angle (Y) at which this muscle reaction is first felt. This method is very time consuming. Therefore it was simplified to the Modified Tardieu Scale (MTS)²⁹. The MTS only defines the moment of the 'catch', seen in the ROM at a particular joint angle at a fast passive stretch.

The third group, 'Other Clinical Grading Scales', is a combination of clinical spasticity assessment scales or tests that can be distinguished from the other two groups, either because of their assessment technique or the method of quantification. A description of all scales is presented in Appendix I.

Some references reported more than one clinical spasticity grading scale. As a consequence, spasticity was clinically assessed 135 times in the 119 included references. 'Ashworth-like scales' were used in 83% (112/135), 'Tardieu-like scales' in 10% (13/135), and 'Other Clinical Grading Scales' in 7% (10/135) of all reports of grading scales. The results will be reviewed for these three groups.

Assessment with different standardized velocities

Of the ‘Ashworth-like scales’, only the original publication of NYU²⁶ described the assessment of each muscle performed by stretching the muscle at two velocities: ‘slow’ and ‘fast’, without further standardization. Of all references reporting on using the NYU, two references^{30,31} confirmed this multiple velocity stretching protocol, whereas two others^{32,33} simply referred to its original publication²⁶. In the other ‘Ashworth-like scales’, as well as in the ‘Other Clinical Grading Scales’, the assessment involves stretching the muscle at only one (non-standardized) velocity.

Of the ‘Tardieu-like scales’, the original publication of the TS²⁸ stated that muscle stretch should be performed at three specified velocities: ‘slow’, ‘under gravity’, and ‘fast’ (without further standardization), referred to as V1, V2, and V3 respectively. Two references^{34,35} reporting on using the TS assessed the muscle stretch only at two velocities of stretch (V1 and V3). The MTS²⁹ was originally described as a muscle assessment at only a fast passive velocity stretch (V3). However, one reference³⁶ reporting on using the MTS described the assessment of muscle stretch at both slow and fast velocity (respectively V1 and V3).

Standardized testing posture of the patient

The original publications presenting the TS²⁸, the MTS²⁹, the NYU²⁶, and the Duncan Ely Test (DET)³⁹ defined a standardized posture of the patient while assessing muscle spasticity. They all emphasized the importance of a consistent position of the patient during assessment, as well as a consistent starting position of the tested limb with the TS and MTS. With the TS, MTS, and the NYU the patient should be assessed in a supine position with the head in midline, although the TS may also be performed sitting. For the DET, quadriceps should be assessed with the patient in a prone position.

Three references^{29,41,42} reporting on using the MTS confirmed supine testing or the use of a standardized testing protocol, whereas most others referred to the original MTS publication²⁹, or to the original publication reporting on the TS²⁸, in

Table 2: Abbreviations and full names of instruments used for clinical assessment of spasticity and their original reference

AS	Ashworth Scale	Ashworth (1964) ²³
MAS-B	Modified Ashworth Scale - Bohannon	Bohannon and Smith (1987) ²⁴
MAS-P	Modified Ashworth Scale - Peacock	Peacock and Staudt (1991) ²⁵
NYU	New York University Tone Scale	Johann-Murphy (1990) ²⁶
TS	Tardieu Scale*	Held and Pierrot-Deseilligny (1969) ²⁸
MTS	Modified Tardieu Scale†	Boyd and Graham (1999) ²⁹
SG	Spasticity Grading	Sindou and Jeanmonod (1989) ³⁷
MCSP	Modified Composite Spasticity Index	Levin and Hui-chan (1992) ³⁸
DET	Duncan Ely Test‡	Bleck (1987) ³⁹
	Nameless clinical grading scale	Trombly (1983) ⁴⁰
	Three nameless clinical grading scales	No references

**Also called 'Held Scale'; †also called 'Dynamic Muscle Length', 'Dynamic Muscle Range', 'Dynamic Range of Motion', or 'R1'; ‡also called 'Ely Test'.*

which a sitting testing posture is also described. One of the references³⁵ reporting on using the TS described assessment of the patient while supine lying; another only assessed the patient in a prone position (triceps surae testing)³⁴. Four references reporting on using the NYU³⁰⁻³³ just referred to the original NYU publication²⁶. All references⁴³⁻⁴⁵ reporting on using the DET described a prone position.

A description of the standardized posture of a patient during testing was lacking in the original publications of the AS²³, the MAS-B²⁴, the MAS-P²⁵, and other 'Other Clinical Grading Scales'. Only 12 of the references reporting on using 'Ashworth-like scales' and one of the references reporting on using 'Other Clinical Grading Scales' described a specified testing posture: 'lying supine' was the most common posture during both lower and upper extremity assessment for the other

‘Ashworth-like scales’⁴⁶⁻⁵⁴. Three references^{42,55,56} in which these scales were reported described a ‘specified’ protocol, but no further details.

Quantification of spasticity

The common feature of all ‘Ashworth-like scales’ is grading the intensity of the muscle tone at one (non-) specified velocity. Even the NYU restricts its grading to a combined score for ROM and muscle tone intensity only at the fast velocity, despite assessment at both a slow and a fast velocity stretch (Appendix I). Over half of the references that reported on using an ‘Ashworth-like scale’ either gave a description of the scoring scale or referred to the original publication, or both. However, inconsistencies exist in the number of scoring options (e.g. MAS-P can be used either as a 5-point or a 6-point scale) as well as in the score ranges. Despite these different applications, the original scoring scales, as presented in Appendix I, are most frequently used.

Both ‘Tardieu-like scales’ grade spasticity by measuring the joint angle at a fast velocity stretch (V3) at which an increase in muscle tone is encountered. The TS is more comprehensive, because it also measures the ROM at a slow velocity stretch, and the joint angle at which an increase in muscle tone is encountered at a moderate velocity stretch. The intensity of the muscle response is also scored on a 5-point scale at each of the three specified velocities. The joint angles measured during the slow and fast velocity stretches are referred to as ‘R2’ and ‘R1’ respectively (Appendix I). Of all the references reporting on using the TS, one³⁴ involved the complete original scoring, and all the others^{36,49} only parts of it. One reference³⁶ reporting on using the MTS measured both the joint angles ‘R1’ and ‘R2’. Two references^{29,126} reporting on using the MTS suggested that the ‘dynamic component’^{6,29} should be used as a clinical measure of spasticity, calculated as the difference between the joint angles R2 and R1. This can easily be calculated with the TS, but also with the MTS if passive ROM is tested.

Apart from the DET³⁹, in which quadriceps spasticity is graded by shown buttock elevation, spasticity grading with the six different ‘Other Clinical Rating Scales’

Table 3: Instruments used for the clinical assessment of spasticity.....

Table 3. Instruments used for the clinical assessment of spasticity.....						
Group and instrument		Publication referred to	Different velocities specified?		Posture specified?	
Ashworth-like scales						
Ashworth scale	(35) ^{5,43,46,57-88}	Ashworth (1964) (22)	N	(35)	N	(34)
		other (40)	Y	(0)	Y	(1)
		none (9)				
Modified Ashworth scale/ Bohannon scale	(60) ^{6,29,36,41,42,47-50,55,56,71,89-125 126-136}	Bohannon (1987) (48)	N	(60)	N	(54)
		other (1)	Y	(0)	Y	(6)
		none (11)				
Modified Ashworth scale/ Peacock Scale	(11) ^{25,51-54,137-142}	Peacock (1987, 1991) (5)	N	(11)	N	(7)
		Bohannon (1987) (5)	Y	(0)	Y	(4)
		none (1)				
Modification of Ashworth: NYU Tone scale	(6) ^{30-33,127,143}	Johann-Murphy (1990) (4)	N	(2)	N	(2)
		Arens and Peacock (1989) (1)	Y	(2+2‡)	Y	(4‡)
		Ashworth (1964) (1)				

* Number of references that specified scoring scale and/or grading scale, but did not define a corresponding response definition.

† Number of references specified a scoring scale and/or grading scale with the corresponding response definition.

‡ Not described in the reference, but reference is made to the original (or another) publication.

N, no; Y, yes; S, scoring scale and/or grading; S + D, scoring scale and/or grading and response definition; V, velocity of stretch; X, muscle reaction to stretch; Y**, joint angle; R1, joint angle at fast velocity passive stretch; R2, joint angle at slow velocity passive stretch; n.e., not extracted. Numbers in brackets are number of references.

..... in children with cerebral palsy

Quantification of spasticity specified?

<i>Specified?</i>		<i>Scoring Scale</i>	
<i>(Ashworth-like scales - continued)</i>			
N	(8)		
Y:S*	(0)	1,2,3,4,5	(9 + 9‡)
Y: S+D†	(27)	0,1,2,3,4	(9)
N	(8)	0-4	(1)
Y:S*	(5)	0-5	(2)
		0,1,2,3,4,5	(1)
		0,1,1+,2,3,4,5	(1)
		0,1,1+,2,3,4	(10+36§)
Y: S+D†	(47)	0,1,2,3,4,5	(1)
N	(0)		
Y:S*	(2)	0,1,2,3,4,5	(1)
		0-5	(1)
Y: S+D†	(1)	0,1,2,3,4	(1)
	(8)	0,1,2,3,4,5	(5+2‡)
		-1,0,1,2,3,4	
N	(1)		
Y:S*	(0)		
Y: S+D†	(4)	-1,0,1,2,3	(3)
		1,2,3,4,5	(1)
	(1)	0,1,2,3	(1)

Table 3: Instruments used for the clinical assessment of spasticity.....

Table 3. Instruments used for the clinical assessment of spasticity.....						
Group and instrument		Publication referred to	Different velocities specified?		Posture specified?	
<i>Tardieu-like scales</i>						
Tardieu scale	(3) ^{34,36,49}	Tardieu (1954, 1983) (2)	N	(0)	N	(1)
		none (1)	Y	(3)	Y	(2)
Modified Tardieu scale	(10) 6,29,36,41,42,47,71,90,99,126	Boyd (1999) (6)	N	(9)	N	(1)
		Tardieu (1954) (2)	Y	(1)	Y	(2)
		Held (1969) (2)				
<i>Other clinical grading scales</i>						
Spasticity Grading	(2) ^{144,145}	none (2)	N	(2)	N	(2)
			Y	(0)	Y	(0)
Modified Composite Spasticity Index	(1) ¹⁴⁶	none (1)	N	(1)	N	(0)
			Y	(0)	Y	(1)
Duncan Ely test	(3) ⁴³⁻⁴⁵	Bleck (1987) (2)	N	(3)	N	(0)
		Gage (1992) (1)	Y	(0)	Y	(3)
Nameless	(4) ^{35,104,147,148}	none (4)	N	(4)	N	(4)
			Y	(0)	Y	(0)

* Number of references that specified scoring scale and/or grading scale, but did not define a corresponding response definition.

† Number of references specified a scoring scale and/or grading scale with the corresponding response definition.

‡ Not described in the reference, but reference is made to the original (or another) publication.

N, no; Y, yes; S, scoring scale and/or grading; S + D, scoring scale and/or grading and response definition; V, velocity of stretch; X, muscle reaction to stretch; Y*, joint angle; R1, joint angle at fast velocity passive stretch; R2, joint angle at slow velocity passive stretch; n.e., not extracted. Numbers in brackets are number of references.

..... in children with cerebral palsy - continued

Quantification of spasticity specified?

<i>Specified?</i>	<i>Scoring Scale</i>		
<i>(Tardieu-like scales - continued)</i>			
N	(0)		
Y:S*	(0)		
Y: S+D†	(3)	X at V?	(1)
		X and Y** at V?	(1)
		X and Y** at V1,V2,V3	(1)
N	(1)		
Y:S*	(0)		
Y: S+D†	(9)	R1	(3+5‡)
		R1 and R2	(1)
<i>(Other clinical grading scales - continued)</i>			
n.e.			
n.e.			
n.e.			
n.e.			

varies from grading muscle tone³⁵, or grading the joint angle in the ROM at which an increase in muscle tone is experienced⁴⁰, to a more complex combination of these or other different parameters^{38,144,147,148} (Appendix I). Because each of these ‘Other Clinical Rating Scales’ was used only once or twice, we did not extract these data.

Discussion

In 119 references, 13 different instruments were used for the clinical assessment of spasticity in children with CP. This review shows that most of these instruments do not comply with the concept of spasticity as defined by Lance: they mostly grade muscle tone intensity only at one (often non-specified) velocity of passive stretch. The references in which these instruments were used seldom standardized the testing posture of the patient. For the quantification of spasticity, most instruments grade the intensity of the muscle tone and ROM. However, the scoring systems of most instruments are ambiguous because different grading and score ranges have been used.

Comparison of research data on the treatment of spasticity is only possible if the exact scoring system has been defined. Only the TS measures the velocity-dependent increase in muscle tone and compares the intensity and the angle of appearance of the increased muscle tone at three different movement velocities. Although the original publication of the NYU reports on the assessment of the muscle at slow and fast velocity stretches, the NYU grading does not comply with the concept of spasticity as its grading is restricted to the fast velocity stretch. The TS describes a very comprehensive method to assess patients, but it seems to be very time consuming. Its feasibility is, therefore, questioned, especially for use with children. This might explain the great variation in test protocols for the

clinical application of this scale in the included references. Simplification of the test protocol is, therefore, desirable.

Although the TS takes the speed of the muscle stretch into account, no standardization of the three different velocities is described in the original publication²⁸. Both the joint angle and the intensity of the muscle response are velocity dependent. Recently, Mackey et al.¹⁴⁹ measured the angular velocities with which the passive stretching of the elbow muscle is performed for assessment with the TS. The results showed great variances in the three angular velocities. To achieve a reliable assessment, it is, therefore, necessary to follow a standardized protocol.

With the TS the intensity of the muscle tone is scored on a 5-point scale (Appendix 1), in which clonus is set to be the highest level of spasticity. However, as shown in Table 1, clonus is another excess symptom that is related to spasticity¹⁵⁰, but not specific for the presence of spasticity. It also differs from spasticity in the muscles in which it can be evoked: clonus can only be evoked in specific muscles, whereas increased muscle tone can be evoked in all muscles.

The TS compares the angle of appearance of the increased muscle tone at three different movement velocities. A measure derived from the TS, used in the literature¹²⁶ as a clinical measure of spasticity, is the 'dynamic component'⁶. This can be calculated as the difference between the joint angle of the passive range of joint movement at a very slow passive stretch (R2) and the joint angle of the catch at a fast velocity stretch (R1). However, the calculated difference adds together the variances of both joint angles, resulting in very wide inter-session variations, as has been demonstrated in a recent study¹⁵¹. Therefore, to evaluate the treatment of spasticity, it is probably better to compare the maximal ROM at a very slow passive stretch before and after treatment and the joint angle of the catch at a fast velocity passive stretch before and after treatment.

Conclusion

According to the definition of spasticity, i.e. a velocity-dependent increase in muscle tone, the instruments that are most frequently used for the clinical assessment of spasticity in children with CP (the 'Ashworth-like scales') do not comply with the concept of spasticity. Only the original Tardieu Scale is a suitable instrument to measure spasticity. However, the original test protocol seems very time consuming, and lacks standardization of the muscle stretch velocities. Moreover, the rating of the intensity of the muscle response is not an exclusive measure of spasticity because it also includes clonus. Further research is needed to develop a clinical spasticity assessment instrument that complies with the concept of spasticity, with a detailed description of specific velocities of passive stretch, positioning of the patient, and grading of spasticity.

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Appendix I: Clinical spasticity grading scales

1. ASHWORTH-LIKE SCALES

Original Ashworth Scale for grading spasticity²³

Grades the resistance encountered in a specific muscle group by means of passively moving a limb through its range of motion at a non-specified velocity.

Score	Description
0	No increase in muscle tone
1	Slight increase in muscle tone giving a catch and release when the limb was moved in flexion or extension
2	More marked increase in muscle tone, but limb moves easily
3	Considerable increase in tone, passive movement difficult
4	Limb rigid in flexion or extension

Modified Ashworth Scale - Bohannon scale for grading spasticity²⁴

Grades the resistance encountered in a specific muscle group by means of passively moving a limb through its range of motion at a non-specified velocity.

Score	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release, or by minimal resistance at the end of the ROM when the affected part(s) is (are) moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by a minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Appendix I: Clinical spasticity grading scales - continued

Modified Ashworth Scale - Peacock scale for grading spasticity²⁵

Grades the resistance encountered in a specific muscle group by means of passively moving a limb through its range of motion at a non-specified velocity.

Score	Grade	Description
0	Hypotonic	Less than normal muscle tone, floppy
1	Normal	No increase in muscle tone
2	Mild	Slight increase in muscle tone, 'catch' in limb movement or minimal resistance to movement through less than half of the range
3	Moderate	Marked increase in muscle tone through most of the range of motion but the passive movement of the affected part is easily performed
4	Severe	Considerable increase in muscle tone, passive movement difficult
5	Extreme	Affected part rigid in flexion or extension

NYU Tone Scale²⁶

Muscle tone is graded by a combination of the resistance encountered in a specific muscle group to a rapid passive stretch, limitation of range of movement and function.

Score	Grade	Description
-1	Hypotonic	Floppy, less than normal tone
0	Normal	Appropriate resistance to passive movement
1	Mildly increased	Minimal resistance to passive movement noted, but does not impair range or function
2	Moderately increased	Moderate resistance to passive movement noted, full range can be achieved but function is hampered by tone
3	Severely increased	Severe resistance to passive movement noted, full range cannot be reached or is difficult to reach, function is severely hampered

Appendix I: Clinical spasticity grading scales - continued

2. TARDIEU-LIKE SCALES

Tardieu Scale or Held Scale²⁸

Spasticity is clinically assessed by passively moving the joint at three specified velocities (V) and rating the intensity and duration of the muscle reaction to stretch (X) and the joint angle (Y) where this muscle reaction is first felt.

<i>Score</i>	<i>Description</i>
<i>Intensity and duration of reflex (X)</i>	
0	No reflex
1	Only visible contraction
2	Contraction with a short catch
3	Contraction lasting a few seconds or fatigable clonus after a few seconds
4	Contraction lasting a few seconds OR infatigable clonus, not even after a few seconds
<i>Velocity of stretch (V)</i>	
1	Slow
2	Under gravity
3	Rapid
<i>Angle in ROM (Y)</i>	Joint angle in degrees at which X was assessed at V

Modified Tardieu Scale²⁹

Defines the moment of the 'catch' (e.g. Tardieu X=3 or X=4) in the range of motion (R1) at a fast passive stretch (Tardieu V3).

R1	Joint angle at a fast stretch (Tardieu V3)
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Appendix I: Clinical spasticity grading scales - continued

3. OTHER CLINICAL GRADING SCALES

*Duncan Ely test*³⁹

Grades buttock elevation in response to rapid passive flexion of the knee while the patient is in prone position.

+	Buttock elevation
-	No buttock elevation

Spasticity Grading (modified from Sindou and Jeanmonod³⁷ by Lazareff et al.¹⁴⁴)

Four parameters are taken into account to evaluate the degree of muscle tone: (1) the degree to which abnormal posture can be reduced by passive mobilization; (2) passive range of motion of the joint; (3) muscle resistance in response to a non-specified velocity stretch; and (4) the disability experienced by the patient.

Score	Grade	Description
0	Absent	
1	Mild	No abnormal posture Normal passive movement No disability
2	Moderate	Abnormal posture, completely reduced by passive mobilization Full range of joint movement Higher muscular tone than in mild grade Moderate disability
3	Marked	Abnormal posture, incomplete reduced by passive mobilization Limited range of joint movement High resistance to muscle stretching Marked disability
4	Severe	Abnormal posture slightly reduced by passive mobilization Severe disability

Appendix I: Clinical spasticity grading scales - continued

Modified Composite Spasticity Index (modified from Levin and Hui-chan³⁸ by Jobin and Levin¹⁴⁶)

Evaluates ankle spasticity by grading the Achilles tendon jerk response and grading the resistance encountered in the ankle muscle by means of passively moving the ankle to dorsiflexion at a moderate speed. Both are added in a Modified Composite Spasticity Index.

<i>Score</i>	<i>Grade</i>	<i>Description</i>
<i>Achilles tendon jerks</i>		
0		No response
1		- No description -
2		- No description -
3		- No description -
4		Maximally hyperactive response
<i>Modified Ashworth Scale</i>		
0		No response
2		- No description -
4		- No description -
6		- No description -
8		Maximally increased resistance
<i>Modified Composite Spasticity Index = Score Achilles tendon jerks + Score Modified Ashworth Scale (double weighted)</i>		
0-4	Mild spasticity	
5-9	Moderate spasticity	
10-12	Severe spasticity	

Appendix I: Clinical spasticity grading scales - continued

*Nameless*⁴⁰

Grades spasticity on the basis of the range of resistance-free moment.

<i>Grade</i>	<i>Description: muscle can be lengthened quickly through most of its range of motion...</i>
Mild spasticity	... with the stretch reflex occurring in the last quarter of the range
Moderate spasticity	...stretch occurs in mid-range
Severe spasticity	...stretch occurs in initial one quarter of the range

*Nameless*¹⁴⁸

Grades elbow spasticity based on the amount of resistance and ease of joint movement at a non-specified velocity.

<i>Grade</i>	<i>Description</i>
Mild	Mild resistance or a catch is felt during a rapid passive extension of the elbow; the movement could be accomplished easily; cases with involuntary elbow flexion on activity are also included in this grade
Moderate	Moderate resistance is felt and the movement could be accomplished only with some difficulty
Severe	Severe resistance is felt and the movement was either accomplished with great difficulty and pain or could be performed only partly

*Nameless*³⁵

Grades the resistance encountered in a specific muscle group by means of passively moving a limb through its range of motion at a fast velocity.

<i>Score</i>	<i>Description</i>
0	Mobilization without difficulty in the whole range of motion
1	Stop, then free mobilization; slight elastic contraction of the muscle
2	Stop, then mobilization against moderate resistance; moderate elastic contraction of the muscle
3	Stop, then mobilization against severe resistance or strong elastic contraction of the muscle

Appendix I: Clinical spasticity grading scales - continued

Nameless¹⁴⁷

Assesses whether spasticity is increased at rest or normal at rest but built up on activity.

<i>Grade</i>	<i>Description</i>
Low	-No description-
Normal	-No description-
High	-No description-
Very high	-No description-

Chapter 3

The Spasticity Test: a clinical instrument to measure spasticity in children with cerebral palsy

Submitted as:

Scholtes VA, Dallmeijer AJ, Becher JG. The Spasticity Test: a clinical instrument to measure spasticity in children with cerebral palsy.

Abstract

Literature has shown the need for a new clinical spasticity instrument in children with cerebral palsy (CP). We adapted the Tardieu Scale to create the Spasticity Test (SPAT). First, the muscle is passively stretched with a slow velocity (≥ 3 seconds) to measure the maximum range of motion (ROM). Then, spasticity is assessed during a passive stretch with fast velocity (< 1 second) to measure the joint angle of the catch (AOC) and to grade the intensity of the muscle resistance. This study describes the feasibility and reliability of the SPAT in five leg muscles. Twenty children with CP (mean age 10 years 0 months, SD 2 years 8 months) were assessed by two examiners on three occasions using a repeated measures design, collecting all data on the same day. Intra-rater reliability was good for the hamstrings, soleus and gastrocnemius muscles, and when the spasticity scale was simplified, also for the adductor muscle, but not for the rectus femoris muscle. Inter-rater reliability was only good for the gastrocnemius muscle. When applied by one examiner, the SPAT was feasible and reliable for all of the investigated leg muscles, except for the rectus femoris muscle.

Introduction

Spasticity is the phenomenon of a velocity-dependent increase in muscle tone in response to passive stretch¹, encountered as resistance somewhere in the range of motion (ROM)². When the angular velocity of the stretch increases, the intensity becomes stronger and appears sooner in the ROM³. This is studied by stretching the muscle with two different velocities, e.g. slow and fast⁴. It is especially important to test spasticity with a fast passive stretch. This makes it possible to detect the dominant phenomenon of spasticity: the 'catch', a sudden appearance of increased resistance in response to a fast passive stretch at a certain angle before the end ROM, which stops the movement immediately^{3,5}. The angle at which the catch is first felt can be measured. Consequently, any measurement to assess spasticity should quantify the intensity of the encountered resistance and measure the angle of the catch (AOC) while passively stretching the muscle with at least a fast angular velocity.

Spasticity is routinely assessed in children with cerebral palsy (CP) by means of clinical scales⁶, of which the Ashworth Scale (AS)⁷ and the Modified Ashworth Scale (MAS)⁸ are most frequently used⁴. However, these scales rate spasticity using an undefined velocity of stretch⁴. Moreover, both have been criticised to be invalid measures of spasticity⁹.

The only clinical scales that measure spasticity with a fast angular velocity are the less frequently used Held Scale (HS)¹⁰ (better known as the Tardieu Scale [TS]) and the Modified Tardieu Scale (MTS)¹¹.

The TS assesses a muscle at three different velocities of passive stretch (e.g. slow, under gravity and fast), and measures the joint angles with goniometry and grades the intensity of the stretch reflex on a 5-point scale (Appendix I) at each velocity. However, although the TS measures spasticity with a fast velocity stretch, there are some limitations to its use. First, the intensity of the stretch reflex scale

implies that a clonus (a score of 3 or 4) is the most severe form of spasticity. However, clonus is a different symptom of the Upper Motor Neuron System⁴ and should be graded separately. Secondly, the TS has some practical disadvantages, such as the lack of standardisation of stretch velocities and joint starting positions and a time-consuming testing protocol⁴.

The MTS only uses the fast velocity stretch from the TS to record the AOC. However, according to its definition, the catch must be experienced somewhere before the end ROM. A prerequisite for its assessment should therefore be that ROM is included in the test, which is not so in the MTS. Moreover, the MTS does not measure the intensity of the encountered muscle resistance.

In conclusion, there is a need for a new clinical spasticity scale which assesses the muscle at both slow and fast velocity stretch. This scale should be well standardised, unambiguous and not time-consuming. We simplified the TS to create the Spasticity Test (SPAT), and the purpose of this paper is to describe the feasibility and reliability of the SPAT in the clinical assessment of spasticity in children with CP.

Methods

Participants

Included in the study were children, between 6 and 17 years of age, with a diagnosis of spastic CP. Exclusion criteria are presented in Table 1.

Children were recruited from a special school for children with physical disabilities in the Netherlands. The Medical Ethics Committee of the VU University Medical Center approved the study. Full written informed consent was obtained from all parents and all children aged 12 years and older.

Table 1: Exclusion criteria

Casting or botulinum toxin A injections within the previous 4 months;
Orthopaedic surgery within the previous 12 months;
Previous Selective Dorsal Rhizotomy or intrathecal baclofen treatment;
Maximum passive ankle dorsiflexion (knee extended) of 15° plantarflexion;
Maximum passive hip extension in prone position of 15° flexion;
Disturbed behaviour that would make it difficult for the child to understand the tests or to cooperate during the study;
Inability to relax during the measurements.

Procedure

The children were tested at school. According to the location of the motor disorder, the affected (unilateral), the most affected (asymmetric diplegia) or the right leg (symmetric diplegia) was tested.

Data was collected during three trials, on the same day, by two examiners. Five leg muscles were assessed in each trial (presented in the order of testing): (medial) hamstrings, short adductors, soleus, gastrocnemius and rectus femoris muscles. Each muscle was tested in a standardised position (Appendix II).

The Spasticity Test (SPAT)

Spasticity is elicited by stretching the muscle at a high angular velocity (< 1 second) and graded by the intensity of the muscle resistance and, when appropriate, the joint angle of the catch. Intensity is graded on a 4-point spasticity scale (0 = normal or increased muscle resistance over the whole ROM; 1 = increase in muscle resistance somewhere in the ROM without a catch; 2 = catch and release; 3 = clear catch, blocking further movement). If the intensity score is 2 or 3, the joint angle of the catch (e.g. score 2: the limb is placed back in the position where the catch first appeared) is recorded with goniometry, and referred to as the Angle of Catch (AOC). If the score is 0 or 1, no AOC can be measured.

Prior to fast stretching the muscle is stretched with very slow velocity stretch (≥ 3 seconds) to record the maximum ROM of each muscle with goniometry. A detailed protocol for the SPAT is presented in Appendix III.

Examiners

One examiner (a researcher, experienced in SPAT assessment) tested each patient twice in two subsequent trials. A second examiner (an experienced paediatric physical therapist, but inexperienced in SPAT assessment) tested each patient once in a third trial. The second examiner studied the written protocol with standardised guidelines beforehand, and one week prior to the study both examiners assessed three children in a practice session. Joint angle measurement (Appendix II) was always performed by an extra observer, trained in goniometry.

Prior to each trial, the child watched a cartoon video for a minimum period of 15 minutes while lying quietly on the research bench in order to enhance relaxation of the child.

The examiners recorded the spasticity scores and the observer recorded the ROM and AOC values on separate scoring sheets, without discussion of results. Between the first and second trial, the child had a 1-hour break in his/her classroom. Between the second and third trial, the child had a 15-min break in the testing room.

Statistical analysis

All analysis were performed in SPSS (11.0) for Windows. Intra-rater reliability was assessed using the first two trials, and inter-rater reliability was assessed using the second and third trial.

The absolute agreement (AA) was calculated for the spasticity scale. For this study, an AA of 70% or higher was considered to be acceptable. The reliability of the ROM and AOC measurements was assessed by calculating the Intraclass Correlation Coefficient (ICC) (< 0.40 = poor; $0.40 - 0.59$ = fair; $0.60 - 0.74$ good; $0.75 - 1.00$ = excellent¹²) and the Standard Error of Measurement (SEM), expressed in degrees. From this, the smallest detectable difference (SDD) was calculated ($1.96 * SEM * \sqrt{2}$)¹³. The SDD is of meaningful interpretive value during the evaluation of therapeutic interventions: the change in an outcome has to be equal to or greater than the SDD to confirm statistically ($p < 0.05$) that the effect of an intervention is detectable in an individual patient.

Results

Ten boys and 10 girls were included in this study. The SPAT was mostly assessed in the right leg ($n=14$). Additional patient characteristics are presented in Table 2.

Table 2: Patient characteristics

<i>Variable</i>	<i>Number</i>	<i>Mean</i>	<i>SD</i>	<i>Range</i>
Location motor disorder (uni:bi)	12 : 8			
GMFCS level (I:II:III:IV)	14 : 3 : 0 : 3			
Age (y:m)		10:0	2:8	4:7 - 14:3
Height (cm)		139	19	108 - 175
Weight (kg)		35.2	13.8	15.0 - 59.0

SD = standard deviation; uni = unilateral; bi = bilateral; y = years; m = months; cm = centimeters; kg = kilogram

Feasibility

The SPAT takes approximately five to eight minutes to perform per limb. At the start of the first trial, six children (30%) said that they felt a little tense, so they were given additional explanation to make them feel at ease and help them to relax. This was successful, and when the third trial started, all the children felt comfortable and were relaxed.

The SPAT was safely used in all children. Two children experienced a slight (unidentified) pain during specific joint testing (one in the ankle during hamstring testing, and the other one in the thigh during rectus femoris testing), but this did not effect the performance of the test. Another child experienced considerable (unidentified) pain in the knee while lying prone, and therefore the rectus femoris of this child was not tested.

Reliability

Table 3 presents the 4x4 contingency tables for the spasticity scale within the first and between the two examiner(s). The results show that the hamstrings, the adductors and especially the calf muscles, are most likely to be affected by spasticity, because the majority of these (80%-100%) had scores of 1, 2 and 3. Overall, grade 3 was most frequently rated (61.9% of all measurements).

The means, standard deviations and ranges for all goniometric measurements (AOC and ROM), as well as the normal average ROMs¹⁴ for all muscles tested, are summarised in Table 4.

Table 5 presents the intra-rater and inter-rater reliability obtained in this study, summarising the AA for the spasticity scale scores, and the ICC, SEM and SDD values for goniometric ROM and AOC testing.

Table 3: Frequency of intra-rater and inter-rater scores on the spasticity scale for the five muscle groups tested

Intra-rater		Examiner 1 (trial 1)																			
		HS				ADD				RF				SOL				GC			
Spasticity scale		0	1	2	3	T	0	1	2	3	T	0	1	2	3	T	0	1	2	3	T
E1	Grade 0	2	0	0	0	2	0	0	0	0	0	5	0	4	1	10	0	0	0	0	0
(t2)	Grade 1	0	0	0	1	1	2	0	0	2	4	1	0	0	0	1	0	0	0	0	0
	Grade 2	0	0	0	1	1	1	0	4	2	7	0	0	4	3	7	0	0	0	1	0
	Grade 3	2	0	1	13	16	0	0	1	8	9	1	0	0	0	1	2	0	1	14	17
	T	4	0	1	15	20	3	0	5	12	20	7	0	8	4	19	2	0	1	17	20
Inter-rater		Examiner 2 (trial 1)																			
		HS				ADD				RF				SOL				GC			
Spasticity scale		0	1	2	3	T	0	1	2	3	T	0	1	2	3	T	0	1	2	3	T
E1	Grade 0	1	0	0	1	2	0	0	0	0	0	6	1	3	0	10	0	1	0	1	2
(t2)	Grade 1	0	0	0	1	1	2	0	2	0	4	0	0	1	0	1	0	0	0	0	0
	Grade 2	1	0	0	0	1	0	1	4	2	7	1	0	0	6	7	0	0	1	0	1
	Grade 3	2	2	2	10	16	1	1	0	7	9	1	0	0	0	1	2	0	4	11	17
	T	4	2	2	12	20	3	2	6	9	20	8	1	4	6	19	2	1	5	12	20

HS = (medial) hamstring muscles; ADD = adductor muscle; RF = rectus femoris muscle; SOL = soleus muscle; GC = gastrocnemius muscle; E1= examiner 1; t2 = trial 2; T= total. Clarification to Table 3: In the first trial, examiner 1 rated 4 out of 20 measured hamstrings as grade 0, 0 as grade 1, 1 as grade 2 and 15 as grade 3. In the second trial, the same examiner rated 2 out of 20 measured hamstrings as grade 0, 1 as grade 1, 1 as grade 2 and 16 as grade 3. The absolute agreement (presented in Table 4) within both trials was $(2+13)/20 = 75\%$

Table 4: Normal average range of motion (ROM)¹⁴ and goniometric measurements (in degrees) of maximum ROM and angle of catch (AOC) for the five muscle groups tested

<i>Muscle tested</i>	<i>n</i>	<i>normal average ROM</i>	ROM			AOC				
			Examiner 1		Examiner 2	Examiner 1		Examiner 2		
			<i>trial 1</i>	<i>trial 2</i>	<i>trial 1</i>	<i>trial 1</i>	<i>trial 2</i>	<i>trial 1</i>		
			<i>mean (SD)</i> <i>range</i>	<i>mean (SD)</i> <i>range</i>	<i>mean (SD)</i> <i>range</i>	<i>n*</i> <i>mean (SD)</i> <i>range</i>	<i>n</i> <i>mean (SD)</i> <i>range</i>	<i>n</i> <i>mean (SD)</i> <i>range</i>	<i>n</i> <i>mean (SD)</i> <i>range</i>	<i>n</i> <i>mean (SD)</i> <i>range</i>
HS	20	140 - 20†	63.8 (12.0) 33 - 85	61.0 (10.7) 32 - 76	55.9 (13.6) 38 - 84	17 86.8 (13.1) 65 - 116	16 81.4 (11.2) 66 - 85	15 73.07 (15.8) 49 - 96		
ADD	20	0 - 60‡	59.55 (11.5) 40 - 80	58.4 (11.7) 35 - 80	58.6 (11.5) 35 - 75	16 32.8 (12.4) 15 - 52	17 36.4 (13.5) 15 - 57	14 33.2 (10.2) 20 - 52		
RF	19	135 - 0†	143.0 (18.5) 85 - 165	140.2 (20.9) 81 - 162	140.3 (21.6) 90 - 163	12 87.8 (27.2) 52 - 127	8 96.1 (27.9) 66 - 146	10 78.6 (22.6) 14 - 113		
SOL	20	(-50) - 20§	17.5 (9.9) 0 - 5	17.2 (10.1) -4 - 38	9.9 (6.0) 1 - 23	18 -5.2 (9.70) -26 - 10	18 -6.8 (8.4) -20 - 12	17 -5.0 (7.0) -21 - 6		
GC	20	(-50) - 20§	8.4 (7.7) -4 - 30	8.1 (9.0) -6 - 29	6.2 (6.6) -4 - 20	20 -10.9 (8.5) -29 - 3	20 -9.3 (8.1) -30 - 0	19 -8.9 (6.5) -25 - -1		

HS = (medial) hamstring muscles; ADD = adductor muscle; RF = rectus femoris muscle; SOL = soleus muscle; GC = gastrocnemius muscle. *number of muscle-measurements in which a catch was registered; †flexion-extension; ‡neutral-abduction; §plantarflexion-dorsalflexion

Intra-rater reliability: ROM

The intra-rater reliability of ROM testing was shown to be excellent (ICC range 0.80 - 0.94) (Table 5), which is also reflected in a reasonably small amount of error (SEM values approximately 3° to 5°). All calculated SDDs were within an acceptable range, i.e. from 7.9° for the adductor and the gastrocnemius to 15.2° for the rectus femoris muscle.

Intra-rater reliability: spasticity scale

The results indicate an acceptable intra-rater agreement for the spasticity grading of the hamstrings, soleus and gastrocnemius muscles (70% - 95%), but poor for the adductor (60%) and rectus femoris muscles (47%). To observe whether one can distinguish the presence of a catch from the absence of a catch, we also converted the spasticity scale to a simplified 2-point spasticity scale, presented in Table 6. On this simplified spasticity scale, agreement increased, and was acceptable for all muscles, except for the rectus femoris muscle (100% for gastrocnemius, 85% for hamstrings and adductor, 80% for soleus and 68% for rectus femoris muscles).

Intra-rater reliability: AOC

The intra-rater reliability of AOC testing was shown to be good to excellent for the hamstrings, adductor and gastrocnemius muscles (ICC range 0.67 - 0.78), and fair for the soleus and rectus femoris muscles (ICC 0.54 and 0.42, respectively). The amount of error was smallest for gastrocnemius testing (SEM 4.8°), and greatest for rectus femoris testing (SEM 18.6°). The resulting SDD calculations were acceptable for the gastrocnemius (13.2°), and for hamstrings, adductor and soleus muscles (range 16.2° - 19.9°). The SDD of the rectus femoris exceeded 50°, which seems poor.

Table 5: Intra-rater and inter-rater reliability for the range of motion (ROM), the spasticity scale, and angle of catch (AOC) measurements for the five muscle groups tested

Intra-rater reliability						Inter-rater reliability					
Muscles tested		ROM						ROM			
		n	ICC	SEM(°)	SDD(°)			n	ICC	SEM(°)	SDD(°)
HS		20	0.80	5.1	14.1			20	0.44	9.5	26.2
ADD		20	0.94	2.9	7.9			20	0.86	4.4	12.1
RF		19	0.92	5.5	15.2			19	0.81	9.2	25.5
SOL		20	0.90	3.1	8.6			20	0.46	7.1	19.8
GC		20	0.88	2.9	7.9			20	0.74	4.0	11.2

Spasticity Scale			AOC				Spasticity Scale			AOC			
			n	ICC	SEM(°)	SDD(°)			n	ICC	SEM(°)	SDD(°)	
	n	AA					n	AA					
HS	20	75%	15	0.69	5.8	19.9	20	55%	13	0.64	6.9	19.2	
ADD	20	60%	15	0.78	7.2	16.2	20	55%	12	0.53	9.7	27.0	
RF	19	47%	6	0.41	18.6	51.4	19	32%	6	-0.48	20.9	57.9	
SOL	20	70%	16	0.54	6.4	17.8	20	60%	16	0.74	4.1	11.4	
GC	20	95%	20	0.67	4.8	13.2	20	65%	19	0.77	3.6	9.9	

HS = (medial) hamstring muscles; ADD = adductor muscle; RF = rectus femoris muscle; SOL = soleus muscle; GC = gastrocnemius muscle; ICC = intraclass correlation coefficient; SEM = standard error of measurement; SDD = smallest detectable difference; AA = absolute agreement

Table 6: The Spasticity Scale and the Simplified Spasticity Scale

<i>Spasticity Scale</i>		<i>Simplified Spasticity Scale</i>
0	= normal <u>or</u> increased muscle resistance over the whole range of motion (ROM)	} 0 = no catch
1	= increase in muscle resistance somewhere in the ROM without a catch	
2	= catch and release	} 1 = catch
3	= clear catch, blocking further movement	

Inter-rater reliability: ROM

The inter-rater reliability of the ROM testing was shown to be good to excellent for the adductors, rectus femoris and gastrocnemius (ICC range 0.74 - 0.86) and fair for the hamstrings and soleus muscles (ICC 0.44 and 0.46, respectively). The amount of error was greatest in the hamstrings and rectus femoris (despite its high ICC) (i.e. SEM values > 9°), and smallest for the adductor and gastrocnemius muscles (i.e. SEM values < 5°). The calculated SDD for the adductor and gastrocnemius are acceptable (12.1° and 11.2°, respectively), but seemed to be inadequate for the hamstrings, rectus femoris and soleus muscles (range 19.8° - 26.2°).

Inter-rater reliability: spasticity scale

The results indicate poor inter-rater agreement (range 32% - 65%) for all muscles. However, if the spasticity grading is simplified (Table 6), agreement increases for all muscles, but only becomes good for the adductor, soleus and gastrocnemius muscles (i.e. 65% for hamstrings, 68% for rectus femoris, 75% for adductor, 85% for soleus, and 95% for gastrocnemius muscles).

Inter-rater reliability: AOC

The inter-rater reliability of AOC testing was shown to be good to excellent for the hamstrings, soleus and gastrocnemius muscles (ICC range 0.64 - 0.77), fair for

the adductor muscle (ICC 0.53), but very poor for the rectus femoris (ICC -0.48). The amount of error was smallest for the gastrocnemius and soleus (SEM 3.6° and 4.1°, respectively), and greatest for the rectus femoris (SEM 20.9°). The SDDs seem to be acceptable for the hamstrings, gastrocnemius and soleus (e.g. all below 20°), but seem to be inadequate for the adductor and rectus femoris muscles (27° and 57.9°, respectively).

Discussion and Conclusion

We developed a new clinical instrument to assess spasticity in the lower limb muscles of children with CP: the Spasticity Test (SPAT). We investigated the feasibility and reliability of the SPAT in order to determine its usefulness in the clinical assessment of children with CP.

The new instrument is named the SPAT (Spasticity Test) to avoid confusion with the Tardieu Scale (TS) and the Modified Tardieu Scale (MTS), from which it is simplified. The SPAT assesses the muscles with two different velocities. It has a detailed written test protocol (e.g. muscle-specific standardised guidelines concerning the stretching velocity, type and number of stretches, starting position for the limbs and testing position of the child¹⁵⁻¹⁷).

The SPAT is easy to perform, and the bilateral examination can be completed within a maximum period of 15 minutes, which makes it feasible for use in clinical practice.

The results show that when one experienced examiner performs the SPAT, the reliability is good for almost all the measured muscles, i.e. the hamstrings, soleus and gastrocnemius muscles, and also for the adductor muscle, provided that the spasticity scale is simplified from a 4 to a 2-point scale. Only the rectus femoris muscle could not be reliably tested with the SPAT, and this muscle should

therefore not be assessed with it. As in other studies, particularly those evaluating joint angles^{18,19}, we found that the intra-rater reliability was considerably greater than the inter-rater reliability for almost all the measured muscles, thus repeated measurements should always be performed by the same examiner. When assessed by two examiners with different levels of experience, the SPAT is only reliable for the gastrocnemius. This is probably due to lack of experience in one of the examiners. Trained examiners can be expected to use the SPAT with a higher degree of reliability²⁰. Before the SPAT can be used in a clinical practice with multiple examiners, this reliability research must be repeated with trained examiners, for whom a specific training programme must be developed.

The SDDs in joint angles varied among the muscles tested. When tested by the same examiner, changes in excess of 8° - 14° in the range of motion (ROM) and in excess of 13° - 20° in the angle of the catch (AOC) would be required to demonstrate with confidence true changes in the soleus and gastrocnemius muscles and hamstrings. The interpretation of the SDD for each muscle is arbitrary. We based it on our clinical experience in which a difference in ROM of approximately 15° in the large muscles (the hamstrings and rectus femoris), and 10° in the smaller muscles (the soleus and gastrocnemius) is found clinically relevant. These are therefore considered to be 'acceptable' SDD's.

For AOC measurements, the SDD is more complicated to interpret. Treatment of spasticity is often based on the extent of the 'dynamic component'¹¹ (absolute difference between ROM and AOC) of the tested muscle. The mean dynamic components in this study were 50° for rectus femoris muscle, 25° for the adductor muscles, and 20° for the other muscles. Except for the rectus femoris muscle, these could all be reliably tested with the SPAT.

Other comparable studies evaluated the reliability of slow and fast joint angle measurements, and found poorer results. Kilgour et al.²¹ concluded that, for both velocities of the stretch, a change of more than 20° between sessions would be required to demonstrate a change in the ROM of the calf and hamstrings muscles.

Fosang et al.²² presented numerous intrarater SEM values for the gastrocnemius and the hamstrings muscle, the means of which (ROM: 4.8° and 6.4° and AOC: 5.5° and 8.5°, respectively) were all higher than the values found in our study. These studies used a less extensive protocol, and our better results might be explained by the detailed written protocol of the SPAT. Still, the variances found in our study were considerably higher for the AOC, compared to the ROM for all muscles. One explanation could be that particularly the fast velocity of stretch was not adequately standardised (see Appendix 2). Despite the written instructions on the fast velocity in the present study, some variation is still expected, as shown in an other study on biceps testing²³.

Angular velocity data was not measured, so we don't know how much the two velocities varied, and whether this influenced the reliability of the SPAT. We hypothesise that better standardisation of the two velocities could increase reliability of the ROM and the AOC. Standardisation could be performed by use of a measurement device (for instance an electro-goniometer) that provides feedback on the angular velocity of the joint excursion.

The reliability of the angular measurements could also have been influenced by the goniometry. To reduce measurement error, bony landmarks were marked for correct placement of the goniometer and assessment was performed by one trained observer according to a standardised protocol.

The SPAT provides relevant clinical information in the evaluation of a single patient, as it is assumed that the level of intensity of the muscle resistance and the AOC reflect the level of spasticity. For example, when the gastrocnemius muscle of a patient is re-assessed after intervention by the same examiner and a clear catch is lowered in intensity from a score of 3 to a score of 0, or appears 15° later in the ROM, one can conclude that there is a decrease in spasticity.

In conclusion, the SPAT is a new and feasible clinical instrument to measure spasticity. It has excellent intra-rater reliability for the hamstrings, soleus and gastrocnemius muscles, and, on condition that the spasticity scale is simplified,

good intra-rater reliability for the adductor muscles. Intra-rater reliability is poor for the rectus femoris muscle. Inter-rater reliability was poor for all muscles, except the gastrocnemius muscle. The results show that repeated SPAT measurements should be performed by the same trained examiner. To improve inter-rater reliability, we suggest that a special training programme should be developed, and that the velocity of the stretch should be further standardised by means of a measurement device.

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Appendix I: Tardieu Scale or Held Scale

Tardieu Scale or Held Scale¹⁰

<i>Intensity and duration of the reflex (X)</i>	<i>Velocity of stretch (V)</i>
0 = no reflex	V1: slow
1 = only visible contraction	V2: under gravity
2 = contraction with a short catch	V3: fast
3 = contraction lasting a few seconds OR fatigable clonus after a few seconds	
4 = contraction lasting a few seconds OR infatigable clonus, not even after a few seconds	Angle in ROM (Y*)

*Spasticity is clinically assessed by passively moving the joint at three specified velocities (V) and rating the intensity and duration of the muscle reaction to stretch (X) and the joint-angle (Y) where this muscle reaction is first felt. *The joint angle at slow velocity is also referred to as R2, the joint angle at fast velocity is also referred to as R1.*

Appendix II: Protocol to measure range of motion and angle of the catch

Protocol for patient and joint positioning to measure the range of motion (ROM) and the angle of the catch (AOC) with goniometry

<i>Muscle</i>	<i>Patient & joint positioning</i>	<i>Maximal ROM and placement of goniometer-arms</i>
HS	Supine: test leg: hip at 90° flexion, knee is extended from a maximally flexed position. Contralateral leg maintained in extension.	Maximal ROM at moment at which the contralateral leg starts to move due to pelvic movement PA: laterally along the long axis of the femur DA: laterally along the long axis of the tibia
ADD	Supine: both hips at 60° flexion, knees at 90° flexion, feet flat. Both knees are abducted from the neutral position.	Maximal ROM at moment of pelvic movement PA: vertically in the mid-position of both SIAS DA: on the upper thigh along the axis of the femur and the mid-patella
RF	Prone: test leg: knee is flexed from a maximal extended position. Contralateral leg maintained in extension.	Maximal ROM at moment of pelvic movement* PA: laterally along the long axis of the femur DA: laterally along the long axis of the tibia
SOL	Supine: test leg: hip and knee flexed at 90°. Foot is dorsiflexed† from maximal plantar flexion. Contralateral leg maintained in extension.	Maximal ROM at maximal dorsal flexion PA: laterally along the long axis of the tibia DA: proximal part of the lateral foot sole
GC	Supine: test leg: from the end ROM position of soleus dorsiflexion, the knee is slowly extended while foot remains dorsiflexed†. Contralateral leg maintained in extension.	Maximal ROM at maximal dorsal flexion PA: laterally along the long axis of the shank DA: proximal part of the lateral foot sole

*HS = (medial) hamstring muscles; ADD = adductor muscle; RF = rectus femoris muscle; SOL = soleus muscle; GC = gastrocnemius muscle; PA = proximal arm; DA = distal arm; SIAS = Spina Iliaca Anterior Superior; *To hinder immediate elevation at beginning of movement the operator's assisting hand stabilises the pelvis by applying pressure to the buttock; †the hindfoot is positioned in neutral varus/valgus and the foot is held in supinated position.*

Appendix III: The Spasticity Test (SPAT)

General Protocol

Child lies down on a research bench with head in midline and arms in anatomical neutral position. Shoes, socks and pants are removed.

Specific starting positions of the joints are defined in Appendix II. The movement is initiated from a maximal possible joint position opposite to the direction of movement.

Child is relaxed during testing.

No pre-stretch is allowed prior to testing.

ROM testing

Stretch the muscle passively to its maximum ROM by applying a very slow stretch in the direction of the end position. The end position is defined as the point at which no further movement is possible, the examiner perceives extensive resistance to stretch, or the child complains of a feeling of discomfort.

Very slow stretch is defined as excursion of the maximum ROM in three or more seconds (counting: one-hundred-and-one, one-hundred-and-two, one-hundred-and-three).

Soft bounced or jerked stretching of the hamstrings and adductors is allowed in the end position. Firm static stretching of the gastrocnemius and soleus is allowed in the end position. Normal static stretching of the rectus femoris is allowed in the end position.

The joint angle of maximum ROM of the 3rd repetitive stretch is measured with goniometry (see Appendix II).

Appendix III: The Spasticity Test (SPAT) - continued

Spasticity testing: measurement of angle of catch (AOC) and grading on the spasticity scale

Stretch the muscle passively towards its maximum ROM by applying a very fast stretch in the direction of the end position.

Very fast stretch is defined as excursion towards the maximum ROM within one second (as fast as possible).

After the 1st stretch with fast velocity, spasticity is graded on a 4-point scale.

Subsequently, if the score is 2 or 3, the angle of the catch (AOC) is measured with goniometry (see Appendix II).

Spasticity scale

Grade	Description
0	normal <u>or</u> increased muscle resistance over the whole ROM
1	increase in muscle resistance somewhere in the ROM without a catch
2	catch and release
3	clear catch, blocking further movement

Ad. 0: normal muscle resistance: not flaccid, not increased

increased muscle resistance over the full ROM: increased resistance to stretch over the full movement; the end ROM is achieved

Ad. 1: increase in muscle resistance somewhere in the ROM without a catch: the resistance to stretch increases in part of movement; the end ROM is achieved

Ad. 2: catch and release: a sudden increase in resistance before the end ROM blocking further movement, after which further movement is possible and the end ROM is achieved

Ad. 3: clear catch, blocking further movement: a sudden increase in resistance before the end ROM blocking further movement, after which no further movement is possible

Chapter 4

Effect of multilevel botulinum toxin A and comprehensive rehabilitation on gait in cerebral palsy

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Abstract

To evaluate the effect of multilevel botulinum toxin A and comprehensive rehabilitation on gait pattern, muscle length, and spasticity, a multicenter randomized trial was performed in 46 children with spastic cerebral palsy who walk with flexed knees. Their mean age was 8.0 years (range 4 to 11 years). They were randomly allocated to the intervention group (multilevel botulinum toxin A and comprehensive rehabilitation) or the control group (usual care). After 6 weeks, a significant treatment effect in the intervention group was observed on: improved knee extension during midstance and terminal swing (7° and 5° , $P < 0.01$, respectively); hip rotation during terminal swing (4° , $P = 0.02$); gait score (1.7, $P < 0.01$); decreased spasticity in hamstrings (11° , $P < 0.01$), gastrocnemius (6° , $P = 0.01$), and soleus (5° , $P = 0.02$); and increased muscle length in hamstrings (9° , $P < 0.01$) and gastrocnemius (5° , $P < 0.01$). The improved muscle length was maintained up to 24 weeks. This study demonstrated that multilevel botulinum toxin A and comprehensive rehabilitation improves knee extension during gait, increases muscle length, and decreases spasticity in injected muscles after 6 weeks in children who walk with flexed knees. Although the effect on muscle length was maintained after 24 weeks, the effect on gait and spasticity had disappeared.

Introduction

Many children with cerebral palsy have a deviating gait pattern. One of the typical patterns that is often observed in cerebral palsy is characterized by flexion of the knee during midstance¹. It has been demonstrated that the natural course of development in these children leads to a further deterioration in this flexion pattern². Because this is generally accompanied by a deterioration in mobility³, treatment is indicated for these children at an early age.

Although the exact cause of the flexion pattern is not known, it is acknowledged that it is attributable to imbalance of the flexor and extensor muscles. It is postulated that this muscle imbalance results from an underlying combination of decreased length of the flexor muscles, decreased strength of the extensor muscles, and abnormal involuntary increased activity of the flexor muscles during gait, such as spasticity⁴. Therefore, in order to improve or prevent further deterioration in the flexion pattern, treatment should focus on restoring these underlying deficits; this requires a comprehensive treatment approach, which should begin with physiotherapy, orthoses, and serial casting. If there is an insufficient response to improve the gait pattern, injection with botulinum toxin A is indicated.

Botulinum toxin A decreases spasticity in the injected muscle and reduces the muscle tone for approximately 8 to 12 weeks⁵. When botulinum toxin A is indicated to improve the gait pattern in children who walk with a flexion pattern, multiple muscle groups should be treated in one session. This method is referred to as multilevel botulinum toxin A treatment. It is generally thought that the reduction in tone in the flexor muscles after multilevel botulinum toxin A injections creates basic conditions that are essential for the further improvement of muscle length and muscle strength in these children. Therefore, to optimize the success of multilevel botulinum toxin A injections, a comprehensive rehabilitation program seems to be crucial. Physiotherapy should be intensified during the pharmacologic period of botulinum toxin A⁶ and aim, in particular, at stretching the flexor muscles, strengthening the extensor muscles, and exercises to improve gait pattern. Serial castings⁷ should be applied to stretch

shortened muscles and thus increase muscle length, and new orthoses should be prescribed to prevent a relapse of muscle shortening and to improve knee extension during stance. Multilevel botulinum toxin A injections followed by such comprehensive rehabilitation may result in an improvement of the gait pattern of these children.

This total treatment package has been standard clinical practice in recent years. A few randomized⁸⁻¹⁰ and nonrandomized studies^{7,11} have evaluated the effect of multilevel botulinum toxin A injections in children with cerebral palsy characterized by various gait patterns. However, little information is available about the effect of multilevel botulinum toxin A on the gait pattern of children who walk with flexed knees. These studies also failed to include a control group receiving usual care. It is important to determine the overall effectiveness of the best clinical practice in these children (multilevel botulinum toxin A plus physiotherapy, orthotics, and, if necessary, serial casting), as opposed to usual care.

The aim of the present study was to measure the effect of lower extremity multilevel botulinum toxin A injections and comprehensive rehabilitation, compared with usual care in ambulatory children with cerebral palsy who walk with flexed knees during midstance. We hypothesized that multilevel botulinum toxin A injections plus comprehensive rehabilitation would decrease knee flexion during gait, decrease spasticity, and improve muscle length.

Methods

Study patients

From October 2001, children were screened for this multicenter trial in four Dutch departments of rehabilitation medicine. The screening included standardized medical history taking and a clinical examination, and frontal and sagittal gait video-recordings with surface electromyography¹². Inclusion was based on consensus between all four participating pediatric physiatrists, reached during a teleconsultation session in which the data collected during screening were discussed via a high-quality video/audio conference¹³. The inclusion and exclusion criteria are listed in Table 1.

Study design and procedure

In this study, the effect of multilevel botulinum toxin A and comprehensive rehabilitation was evaluated on the technical outcome measures: gait pattern, muscle length, and spasticity. Outcomes on mobility and energy cost are described elsewhere¹⁶. This study was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam. Full written informed consent was obtained from all parents and 12-year-old children before enrolment. The children were randomly assigned to one of two groups. The intervention group received multilevel botulinum toxin A injections followed by intensive physiotherapy, orthoses, and, if necessary, serial casting. The control group continued with usual care (low-intensity physiotherapy, 1-2 sessions of 30-60 minutes a week; some used orthoses). The children in the control group were also indicated to receive multilevel botulinum toxin A injections after the control period.

Table 1: Inclusion and exclusion criteria

<i>Inclusion criteria</i>	<i>Exclusion criteria</i>
Diagnosis of cerebral palsy	Botulinum toxin A treatment in lower extremities
Spastic hemiplegia or diplegia (according to Hagberg ¹⁴)	within 16 weeks before inclusion
Age between 4 and 12 years	Orthopedic surgery within 24 weeks before inclusion
Spasticity in two or more lower extremity muscle groups interfering with mobility	Contraindication for botulinum toxin A
Able to walk independently, with or without walking aids	Contraindication for general anesthesia
Gait characterized by persistent flexion of the knee ($\geq 10^\circ$) in midstance (barefoot or with ankle-foot orthoses/shoes)	Orthopedic deformities which have a bad influence on walking:
Two or more muscle groups in one limb requiring botulinum toxin A injection	hip (sub)luxation with migration index ¹⁵ $> 50^\circ$
Able to carry out instructions	hip endorotation contracture $> 15^\circ$
Adequate knowledge of the Dutch language	flexion contracture of knee $> 15^\circ$
	Severe fixed contractures:
	age < 8 years
	ankle dorsiflexion with knee extended $> -20^\circ$
	popliteal angle $> 90^\circ$
	age ≥ 8 years
	ankle dorsiflexion with knee extended $> -15^\circ$
	popliteal angle $> 80^\circ$
	Presence of ataxia or dyskinesia
	Other problems which have a negative influence on walking

Intervention

A consent treatment plan was formulated for each child before randomization, during the teleconsultation session. This plan included target muscle identification, calculation of the injection dosage, the need for serial casting, and the prescription of ankle-foot orthoses.

Botulinum toxin A injections

Possible target muscles were the psoas, medial/lateral hamstrings, hip adductors, rectus femoris, gastrocnemius, soleus, and tibialis posterior muscle. Muscle identification was based on the criteria listed in Table 2. The injections were administered under general anesthesia, in at least two sites per muscle belly, to a maximum of 50 U/site, with a dosage of 4-6 U/kg body weight botulinum toxin A (Botox; Allergan, Nieuwegein, the Netherlands) per muscle group. The maximum total dose was set at 25 U/kg body weight for children ≤ 5 years, and 30 U/kg body weight for children > 6 years, with a maximum recommended dose of 600 U. A dilution of 50 U in 1 mL 0.9% NaCl solution was used. Injection sites were determined by palpation of the muscle belly, and needle placement was verified either by stretching or electric stimulation of the muscle.

Intensive physiotherapy

Beginning 1 week after the multilevel botulinum toxin A injections, the children received treatment 3-5 times a week for 12 weeks from a physiotherapist, according to a standardized treatment protocol. Each session lasted for 45-60 minutes, and the treatment consisted of active and passive stretching of the flexor muscles, strength training of the extensor muscles, functional mobility training, and gait pattern training.

Orthoses

To support full knee-extension in terminal stance, either stiff insoles or ankle-foot orthoses were prescribed.

Serial casting

If the passive ankle dorsiflexion with extended knee measured during screening was less than 0°, serial casting was initiated 1-3 weeks after the injection. Bilateral below-knee walking casts were applied, and changed every week until $\geq 0^\circ$ of dorsiflexion was achieved.

The intervention group had one baseline assessment, and three follow-up assessments at 6, 12, and 24 weeks after multilevel botulinum toxin A injection. The control group had two assessments with a mean interval of 24.61 weeks (SD 5.7; range 18-30).

Gait analysis in the intervention group was performed only at baseline, and 6 and 24 weeks after multilevel botulinum toxin A injection.

Outcome measures

Gait was analyzed from standardized videorecordings of gait in both frontal and sagittal planes while the child walked barefoot, with or without a walking aid. The children were instructed to walk at a comfortable walking speed along a level 10-meter walkway. The gait pattern was qualitatively evaluated according to the Edinburgh Visual Gait Analysis Interval Testing (GAIT) scale¹⁷, which is a biplane video-based scoring scale, developed to assess children with cerebral palsy. It measures 17 joint angles or movements of the trunk and the lower limbs during a representative stride. These 17 items are scored on a 3-point scale: 0 (normal kinematics), 1 (moderate deviation), and 2 (marked deviation). The scores are added together to obtain a GAIT total score, ranging from 0 to 34 points for each

lower limb. In addition to the GAIT total score, knee angle at midstance, ankle angle at midstance, knee angle at terminal swing, and hip rotation at terminal swing were measured. The measurement of joint angles from video-tapes with a digital screen goniometer was performed by one independent research student, who had no knowledge of the moment of assessment. The videotapes were analyzed randomly, and each limb was scored separately.

Table 2: Target muscle identification for botulinum toxin A injections based on gait analysis and clinical examination in children with cerebral palsy who walk with flexed knees

<i>Muscle</i>	<i>Criteria observed during gait analysis</i>	<i>Criteria observed during clinical examination</i>
Psoas	<input type="checkbox"/> increased flexion of the hip during terminal stance, AND <input type="checkbox"/> anterior tilt of the pelvis during terminal stance OR <input type="checkbox"/> increased flexion of the hip during terminal stance, AND <input type="checkbox"/> retraction of the pelvis during terminal stance	
Medial hamstrings*	<input type="checkbox"/> increased flexion of the knee during midstance, AND <input type="checkbox"/> muscle activity [†] of the hamstrings during midstance OR <input type="checkbox"/> increased flexion of the knee during midstance, AND <input type="checkbox"/> endo-adduction rotation of the hip during terminal swing, OR <input type="checkbox"/> increased flexion of the knee during terminal swing, OR <input type="checkbox"/> posterior tilt of the pelvis during terminal swing	& <input type="checkbox"/> spasticity in medial hamstring muscle
Rectus femoris	<input type="checkbox"/> decreased progression to flexion of the knee joint during pre-swing and initial swing, AND <input type="checkbox"/> muscle activity of the rectus femoris during pre-swing	& <input type="checkbox"/> spasticity in the rectus femoris muscle

Table 2: Target muscle identification for botulinum toxin A injections based on gait analysis and clinical examination in children with cerebral palsy who walk with flexed knees - continued

<i>Muscle</i>	<i>Criteria observed during gait analysis</i>		<i>Criteria observed during clinical examination</i>
Biceps femoris	equal to medial hamstrings	&	<input type="checkbox"/> biceps femoris muscle is responsible for decreasing the popliteal angle of $\leq 90^\circ$
Adductor	<input type="checkbox"/> adduction of the hip during swing and stance phase, AND <input type="checkbox"/> endorotation of the hip during swing and stance phase	&	<input type="checkbox"/> spasticity in the adductor muscle
Gastrocnemius	<input type="checkbox"/> muscle activity of the gastrocnemius during midstance	&	<input type="checkbox"/> decreased length [‡] of the gastrocnemius muscle (maximum ankle dorsiflexion with knee extended $\geq 0^\circ$)
Soleus	<input type="checkbox"/> plantar flexion of the ankle during stance phase	&	<input type="checkbox"/> decreased length of the soleus muscle (maximum ankle dorsiflexion with knee 90° flexed $\geq 0^\circ$)
Tibialis posterior	<input type="checkbox"/> varus/adduction/supination of the forefoot AND <input type="checkbox"/> lateral sway of the knee during midstance or terminal stance	&	<input type="checkbox"/> spasticity in the tibialis posterior muscle, AND <input type="checkbox"/> signs of overload (e.g. callus) on the lateral border of the foot

All the criteria must be present to identify that muscle for botulinum toxin A injection.

** Semitendinosus, semimembranosus with gracilis.*

† Muscle activity is measured by means of electromyography.

‡ Muscle length is measured by means of goniometry (see Table 4).

The observer followed the recommended conditions to optimize reliable visual assessment, by including split-screen video-analysis with slow speed viewing and specific training in normative values of gait parameters^{18,19}. Intra-observer reproducibility of the GAIT scale and additional kinematic measurements was established through repetitive scoring of 5% of all videos.

Muscle length and spasticity were measured in hamstrings, adductors, rectus femoris, soleus, and gastrocnemius muscles. Muscle length was tested by assessing the range of motion at slow passive stretch (>3 seconds) while the child was relaxed. The range of motion of the third passive stretch was measured. Spasticity was then measured by assessing the joint angle at which a 'catch' (defined as a sudden increase in muscle tone blocking further movement) occurred in response to a single fast passive stretch (<1 second). Muscle length and spasticity measurement of all children were performed by the same experienced investigator, whereas the joint angles were measured with a standard goniometer by a second investigator. The protocol of the American Academy of Orthopedic Surgeons²⁰ was followed for the positioning of the child and the goniometry for testing each specific muscle group.

Statistical analysis

Group characteristics were tested for differences with the Student t test or the chi-square test. To study the effect of the treatment, the changes from baseline at Weeks 6, 12, and 24 in the intervention group were compared with the effect of usual care in the control group. We studied the treatment effect at 6 weeks postinjection, because the pharmacologic effect of botulinum toxin A was likely to be maximal at this stage. Further analysis was performed at 12 weeks (muscle length and spasticity only) and 24 weeks to assess the duration of the effect.

In the intervention group, the limbs that had been injected with botulinum toxin A were analyzed, and in the control group we analyzed the limbs that would be injected with botulinum toxin A after the control period. Although all outcomes were assessed

for both limbs separately, we chose to report the results of the right and left limbs together, because no significant differences were evident between right and left.

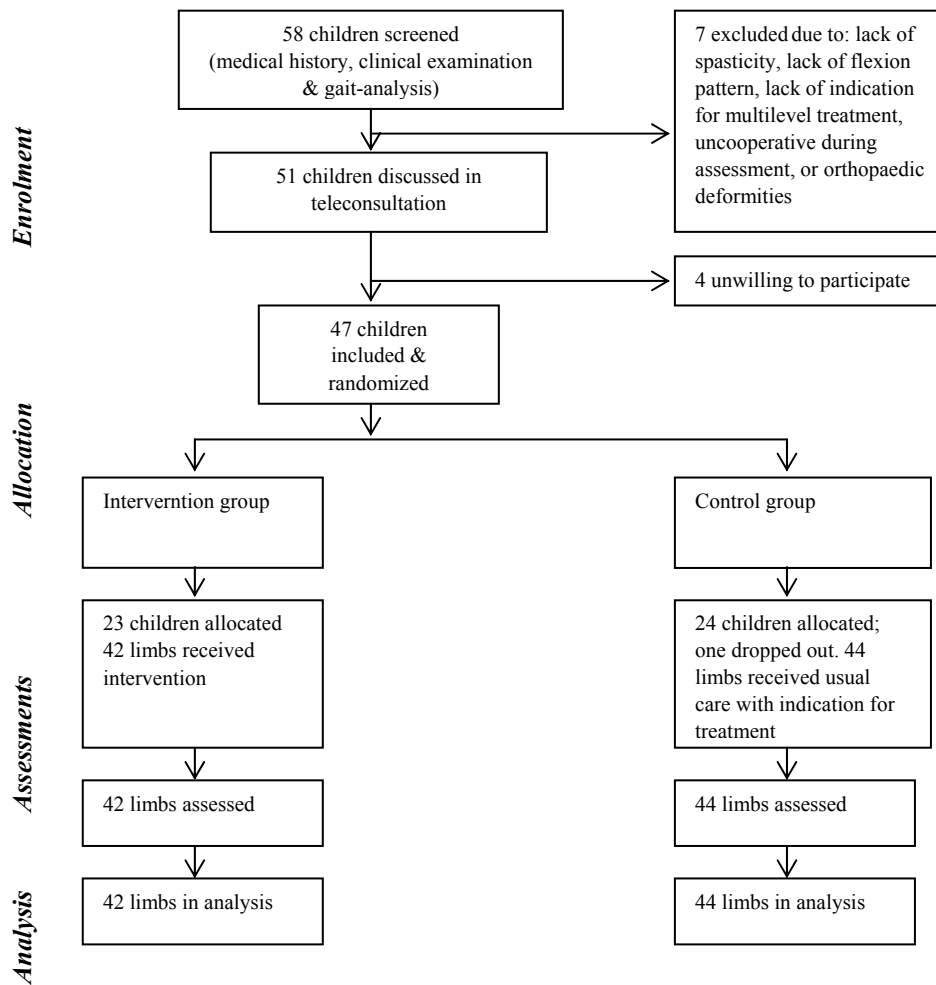
All differences in effect between the intervention and the control group were analyzed in a linear mixed model analysis^{21,22} (SPSS 11.5), which estimated the treatment effect on the different outcome measures. A three-level model (children, limb, and observation) was used to adjust for dependency of repeated observations and left and right limbs in each subject. The factor ‘center’ (center of inclusion and assessment) was taken into account in all statistical analyses.

The intraclass correlation coefficient was used to describe the intra-observer reproducibility of the GAIT total score and kinematic parameters. All analyses were performed by a statistician (D.K.) and the principal investigator (V.S.). The level of statistical significance was set at $P < 0.05$, and all P values were two-sided.

Results

During an intake period of 19 months, 58 children were screened and 47 were included in the study. The selection and randomization procedures are presented as a graph in Figure 1. In the control group, one child dropped out after the first baseline assessment at the request of the parents. This child was excluded from all analyses. The groups did not differ with regard to the personal characteristics summarized in Table 3. In the intervention group, 42 limbs were treated with botulinum toxin A. The most frequently targeted muscles were medial hamstrings, psoas, and gastrocnemius, in varying combinations: 9 limbs (21%) were injected in the medial hamstrings and gastrocnemius; 18 (43%) were injected in the psoas and

Figure 1: Schematic design of selection and randomization



medial hamstrings; 9 (19%) were injected in the psoas, medial hamstrings, and gastrocnemius. Other muscles that were injected (alone or in combination) were lateral hamstrings, rectus femoris, soleus, adductors, and tibialis posterior. All children received multilevel injections in at least one of their limbs. A mean dose of 18.01 U/kg body weight (SD 4.74) was injected, ranging from 5.63 to 27.14 U/kg.

Baseline Differences

The groups did not differ with regard to the personal characteristics summarized in Table 3. The difference between the two groups in terms of age and weight was assessed with the Student t test; the difference in sex, diagnosis, and gross motor function classification system level was assessed with chi-square tests.

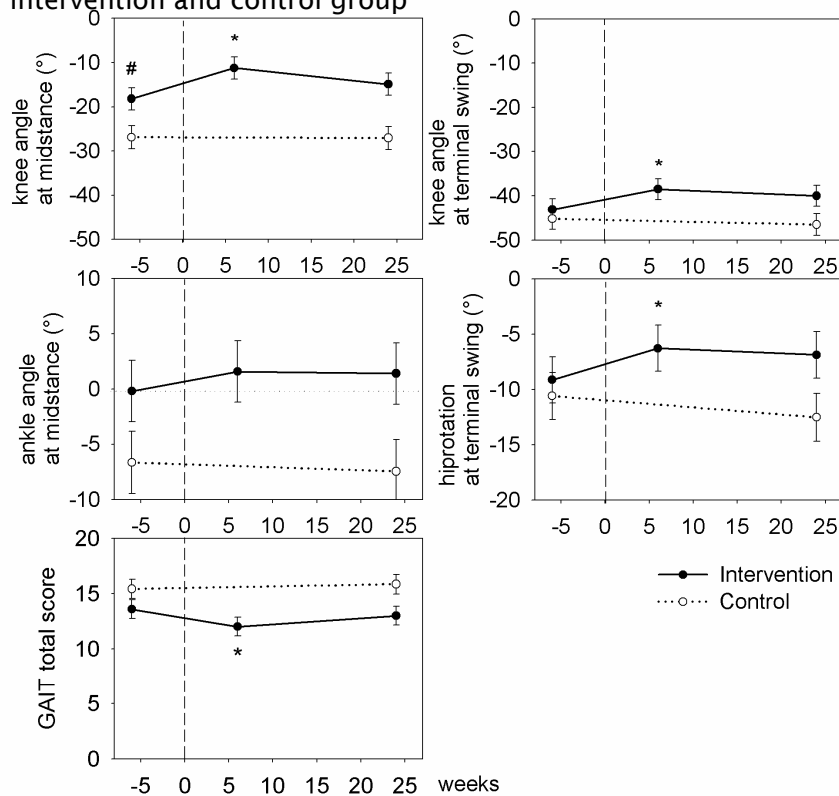
Table 3: Characteristics of all participating children

<i>Group</i>	<i>Age (yr)</i> <i>mean ± SD</i> <i>[range]</i>	<i>Weight (kg)</i> <i>mean ± SD</i> <i>[range]</i>	<i>Sex (n)</i> <i>males:</i> <i>females</i>	<i>Diagnosis</i> <i>(n)</i> <i>uni : bi</i>	<i>GMFCS level</i> <i>(n)</i> <i>I :II :III :IV</i>	<i>ml-BTX-A, (U)</i> <i>mean</i> <i>± SD</i> <i>[range]</i>
Intervention (n = 23)	8.13 ± 2.25 [4.15 to 11.45]	26.76 ± 7.63 [15.00 to 45.00]	16 : 7	3 : 20	9 : 3 : 10 : 1	442.83 ± 132.84 [180 to 710]
Control (n = 23)	7.88 ± 2.25 [4.45 to 11.00]	25.59 ± 8.27 [13.00 to 44.00]	16 : 7	1 : 22	9 : 4 : 7 : 3	

Abbreviations: bi: Bilateral; GMFCS: Gross motor function classification system²³; ml-BTX-A: Multilevel botulinum toxin A; U: Units; uni: Unilateral

No significant differences were found between the intervention and the control group at baseline with regard to the gait parameters, except for the knee angle at midstance ($P < 0.01$), which was significantly worse in the control group (Fig 2). No significant differences in muscle length or the level of spasticity were observed at baseline between the two groups (Fig 3). The estimated mean differences in change between the intervention and the control group with regard to gait parameters, muscle length, and spasticity are presented in Table 4.

Figure 2: Estimated mean values in knee, hip, and ankle angles and Edinburgh Visual Gait Analysis Interval Testing (GAIT) scale total score during gait in intervention and control group



#A significant difference at baseline; *A significant difference in change from baseline between the two groups. Dashed line demarks the moment of botulinum toxin A injections in the intervention group. On the horizontal axis: weeks are before/after botulinum toxin A injections in intervention group. On the vertical axis: negative values indicate flexion on knee angles, plantar flexion on ankle angle, and internal rotation on hip rotation. Positive values indicate dorsal flexion on ankle angle.

Gait parameters

GAIT indicated substantial to good intra-observer reliability with an intraclass correlation coefficient of 0.88. Kinematic parameters exhibited substantial to good intra-observer reliability with an intraclass correlation coefficient of 0.90 for knee angle at midstance, 0.88 for ankle angle at midstance, 0.77 for knee angle at terminal swing, and 0.74 for hip rotation at terminal swing.

After 6 weeks there was a significant treatment effect (Table 4) on the knee angle at midstance (7.0° , $P < 0.01$), knee angle at terminal swing (5.2° , $P < 0.01$), hip rotation at terminal swing (3.6° , $P = 0.02$), and GAIT total score (-1.7 point, $P < 0.01$). Secondary analysis indicated that 17 of the 23 children (74%) in the intervention group improved more than 5° in knee extension of at least one limb, as opposed to 7 of the 23 in the control group (30%) ($P = 0.004$). Two children (9%) in the intervention group, as opposed to 6 in the control group (26%), deteriorated more than 5° in knee flexion.

Figure 2 reveals that the significant differences in effect after 6 weeks mainly result from improvement in the intervention group, whereas the control group manifested no change. No significant treatment effect was observed on the ankle angle at midstance. Improvement in gait pattern was not maintained at 24 weeks after the injections.

Muscle length

At 6 weeks after the injections, there was a significant treatment effect on the muscle lengths of the hamstrings ($P < 0.01$) and gastrocnemius ($P > 0.01$), which was maintained at 12 weeks ($P = 0.02$ and $P = 0.03$ respectively) and 24 weeks ($P < 0.01$ and $P < 0.01$ respectively). Furthermore, a significant treatment effect on the muscle length of the soleus was present at 12 weeks ($P = 0.03$). Figure 3 indicates that the significant differences in effect mainly result from muscle length improvement in the intervention group, whereas in the control group there was no change or a slight deterioration. There was no significant treatment effect on the rectus femoris and the adductor muscle, although there was a tendency for improvement in adductor muscle; this did not reach significance ($P = 0.05$) at 6 weeks (Table 4).

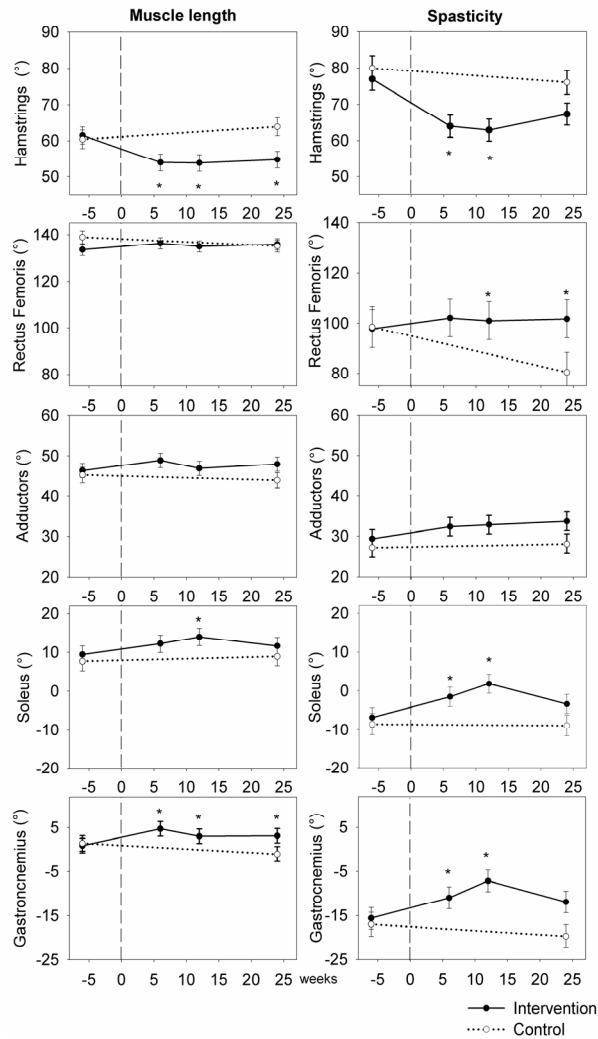


Figure 3: Estimated mean values in muscle length and spasticity of five leg muscles in intervention and control groups

Muscle length was measured by assessing the range of motion during a slow passive stretch. Spasticity was measured by assessing the angle of occurrence of the catch during a fast passive stretch. *A significant difference in change from baseline between the two groups. Dashed line demarks the moment of botulinum toxin A injections in the intervention group. On the horizontal axis: weeks are before/after botulinum toxin A injections in the intervention group. On the vertical axis: negative values indicate plantar flexion in the soleus and gastrocnemius muscle, whereas positive values indicate dorsal flexion.

Table 4: Effect (estimated mean differences in change between intervention and control group) on gait parameters, muscle length, and spasticity

	<i>Week</i>	<i>Effect (95% CI)</i>	<i>P Value</i>
<i>Gait parameters</i>			
Knee angle midstance (°)	6	7.03 (3.76 to 10.30)	<0.01
	24	3.62 (−1.01 to 8.24)	0.12
Knee angle terminal swing (°)	6	5.15 (1.91 to 8.38)	<0.01
	24	4.44 (−0.14 to 9.01)	0.06
Hip rotation terminal swing (°)	6	3.63 (0.58 to 6.67)	0.02
	24	4.18 (−0.12 to 8.48)	0.06
Ankle angle midstance (°)	6	2.08 (−1.63 to 5.80)	0.27
	24	2.40 (−2.85 to 7.62)	0.37
GAIT	6	−1.74 (−2.76 to −0.72)	<0.01
	24	−1.02 (−2.47 to 0.43)	0.17
<i>Muscle length</i>			
Hamstrings (°)	6	−8.87 (−12.87 to −4.88)	<0.01
	12	−9.68 (−14.24 to −5.12)	<0.01
	24	−10.10 (−16.12 to −4.08)	<0.01
Rectus femoris (°)	6	4.26 (−0.63 to 9.15)	0.09
	12	3.71 (−1.83 to 9.29)	0.19
	24	6.19 (−1.16 to 13.54)	0.10
Adductors (°)	6	3.10 (−0.05 to 6.25)	0.05
	12	1.34 (−2.25 to 4.94)	0.46
	24	2.94 (−1.80 to 7.69)	0.22
Soleus (°)	6	2.28 (−0.79 to 5.36)	0.14
	12	3.82 (0.30 to 7.33)	0.03
	24	0.94 (−3.71 to 5.59)	0.69
Gastrocnemius (°)	6	4.76 (2.04 to 7.47)	<0.01
	12	3.57 (0.47 to 6.67)	0.02
	24	4.66 (0.57 to 8.75)	0.03

Table 4: Effect (estimated mean differences in change between intervention and control group) on gait parameters, muscle length, and spasticity - continued

	Week	Effect (95% CI)	P Value
<i>Spasticity</i>			
Hamstrings (°)	6	-11.40 (-17.37 to -5.43)	<0.01
	12	-11.68 (-18.50 to -4.87)	<0.01
	24	-5.70 (-14.70 to 3.30)	0.21
Rectus femoris (°)	6	11.50 (-0.25 to 23.26)	0.06
	12	14.02 (0.59 to 27.45)	0.04
	24	21.98 (4.23 to 39.72)	0.02
Adductors (°)	6	2.62 (-1.37 to 6.62)	0.20
	12	2.92 (-1.63 to 7.48)	0.21
	24	3.41 (-2.61 to 9.42)	0.27
Soleus (°)	6	5.45 (0.69 to 10.21)	0.02
	12	8.88 (3.45 to 14.31)	<0.01
	24	3.81 (-3.37 to 10.99)	0.30
Gastrocnemius (°)	6	5.69 (1.40 to 9.98)	0.01
	12	10.03 (5.12 to 14.93)	<0.01
	24	6.31 (-0.18 to 12.80)	0.06

Positive values indicate increased extension on knee angles; increased external rotation on hip rotation; increased dorsal flexion on ankle angle; increased muscle length and decreased spasticity on rectus femoris, adductors, soleus, and gastrocnemius. Negative values indicate improved gait pattern on GAIT, increased muscle length and decreased spasticity on hamstrings.

Abbreviations CI: Confidence interval; GAIT: Gait Analysis Interval Testing scale total score

Spasticity

At 6 weeks there was a significant treatment effect on spasticity in the hamstrings ($P > 0.01$), soleus ($P = 0.02$), and gastrocnemius ($P = 0.01$) muscles, which was maintained at 12 weeks after the injections (all $P > 0.01$), but not at 24 weeks after the injections. There was a significant treatment effect on spasticity in the rectus femoris muscle at 12 ($P = 0.04$) and at 24 weeks ($P = 0.02$). Figure 3 reveals that these significant differences in effect mainly result from a decline in spasticity in the intervention group, whereas the control group manifested no change or a slight increase, except in the

rectus femoris muscle, which was the result of an increase in spasticity in the control group (Fig 3). No significant treatment effect was observed on the adductor muscle.

Discussion

This randomized clinical trial evaluated the effect of treatment with multilevel botulinum toxin A and comprehensive rehabilitation on gait pattern, muscle length, and spasticity in children with cerebral palsy who walked with flexion of the knee in midstance. The study demonstrated that multilevel botulinum toxin A injections in the hamstring muscle, in some combination with the psoas and gastrocnemius muscle, followed by intensive rehabilitation, significantly improved the knee extension during midstance and terminal swing and hip rotation during terminal swing. It also improved the overall quality of the gait pattern towards a more 'normal' gait. The efficacy of the treatment in reducing muscle shortening and spasticity was also demonstrated.

An improvement in gait kinematics and the quality of the gait pattern assessed according to the GAIT scale was documented at 6 weeks after the injections. At the commencement of this study, the children in the intervention group had a mean knee flexion of 20°, and this was prevented from deterioration. It is known from the literature that that flexed-knee gait has a substantial effect on gait energy expenditure²⁴, and that knee angles beyond 20° flexion considerably impair the ability to walk²⁵. So it is clinically important to prevent these children from any deterioration. The mean improvement of 7° in knee extension during midstance in barefoot walking that was found in this study is similar to the results found after 2 weeks in other uncontrolled studies in which children received hamstrings injections to improve knee extension²⁶⁻²⁸. Moreover, significantly more children in the intervention group had an increase in knee extension compared with the control group. Therefore, we believe that the results of the present study indicate a clinically meaningful improvement in flexed knee gait.

We found no evidence of maintained effect on gait after 24 weeks, contrary to the reports of Cosgrove et al.²⁷, who reported an effect that was maintained up to 26 weeks; however, they did not include a control group. In the present study, gait analysis was only performed at 6 and 24 weeks. However, it is likely that the effect wears off somewhere in between, and that the assessment at 24 weeks was too late to demonstrate sustained improvements. The effect of ankle-foot orthoses on walking was not measured in the present study.

Although our randomization procedure yielded no differences in patient characteristics, and no differences were evident between the two groups in muscle length and level of spasticity, in the control group there was significantly more knee flexion at baseline. Because we do not know the exact influence of this, the results of this study apply at least to children with ranges of knee flexion that are comparable with those in the intervention group.

In the present study, muscle shortening was not included in the exclusion criteria, although it has been suggested by many authors that this is a contraindication for botulinum toxin A treatment. This, despite the fact that desired improvements are only to be expected in muscles that have a reduced range of motion at baseline (thus muscle shortening), and not in muscles that have a full range of motion. At baseline, the patients in the present study manifested moderate muscle shortening in the hamstrings (mean 60.58°) and mild shortening in the gastrocnemius (mean 1.37°) and soleus muscles (mean 10.29°), but full length in the rectus femoris (mean 136.57°) and adductor muscles (mean 45.90°). As expected, the results of this study did produce the desired significant improvement in the length of hamstrings and gastrocnemius muscles on all assessments, and also in the soleus at 12 weeks, but not in the rectus femoris or adductors. Additionally, the muscles that were the main target of botulinum toxin A injection in this study were the hamstrings and gastrocnemius muscles, and these were found to improve shortly after the injections. Because children with muscle shortening were excluded from the other studies, it is not easy to compare our results with those of other studies. However, the study demonstrated that an improvement in muscle lengths can be maintained up to 24 weeks after treatment in shortened

muscles, and therefore mild to moderate muscle shortening does not seem to be a contraindication but, in fact, an indication for treatment.

A reduction in spasticity was observed in the muscles that were most frequently the target for botulinum toxin A injections (i.e., the hamstrings and gastrocnemius) at 6 weeks after the injections and lasting up to 12 weeks. This finding could be expected owing to the pharmacologic mechanism of botulinum toxin A, which blocks signal transmission at the neuromuscular junction by preventing the release of acetylcholine. After approximately 3 months the neuromuscular junction is restored, as a result of sprouting at the nerve end, so the lack of significant findings at 24 weeks supports this temporary effect on spasticity.

Although the soleus was not a target muscle in the patient group, its spasticity also decreased significantly. Because the gastrocnemius and soleus muscles are anatomically near to each other, the reduced spasticity may be due to diffusion of botulinum toxin A. This diffusion to adjacent muscles has also been reported in studies in which hand²⁹ or neck³⁰ muscles have been treated with botulinum toxin A.

The results of other randomized studies lack agreement on the effect that botulinum toxin A has with regard to decreasing spasticity^{9,31,32}. However, although most previous studies used the (Modified) Ashworth Scale to assess spasticity, many researchers have recently stated that the Ashworth is not a valid measure of spasticity³³⁻³⁵, and that it does not acknowledge the velocity dependency of spasticity³⁶ defined by Lance³⁷. We therefore added a velocity component, by measuring the joint angle in response to a slow passive muscle stretch (range of motion), followed by the joint angle at which an increase in muscle tone is encountered in a fast passive muscle stretch, comparable to the modified Tardieu Scale³⁸. This method has been demonstrated to be valid in clinical practice for the measurement of spasticity³⁹, making it possible to detect subtle intervention effects, as also reported in comparable studies^{38,40}.

There were varying intervals between the measurements in the control group. These varying intervals were unavoidable because we had to find a balance between what was scientifically desirable, practically achievable, and clinically necessary: if treatment was planned during the holidays, or if a child complained of pain, the

physician decided to provide the multilevel botulinum toxin A treatment earlier. An interval of 18 weeks was therefore set as a minimum in the control group. As a consequence, the mean duration between the first and the last assessment differed between the two groups, from 24 weeks in the control group to 28 weeks in the intervention group. Using the linear mixed model analysis, we adjusted for this time discrepancy by extrapolating the changes during the assessment period in the control group. It is unlikely that this has influenced our results, because stable baseline values were found in the control group for all outcome measures.

In this multicenter study, multiple assessors performed the measurements. To standardize the treatment and the assessment methods, training sessions were organized before the study. The study was only partially blinded. One single assessor, who was blinded for the moment of assessment, scored the gait-analysis from videos. The intra-rater reliability of the GAIT scale in the present study was good, similar to that reported in a recent study⁴¹, and the intra-rater reliability of the kinematic parameters was substantial to good. We used an observational assessment based on videotapes, rather than the more objective three-dimensional gait analysis, because the latter method was not available in all of the participating rehabilitation centers. In a recent study⁴² video-based scoring of sagittal knee position during midstance was compared with three-dimensional gait analysis and demonstrated to be highly correlating, indicating high validity.

The other assessments were not blinded. It is unlikely that this lack of blinding had a negative influence on our results, because the assessors were not aware of the results of previous assessments.

Many randomized and nonrandomized studies have evaluated the effect of botulinum toxin A treatment for the lower extremities in children with cerebral palsy, but only a few included children with flexed knee gait, despite the risk of deterioration these children have to face when they grow up. Because of the underlying muscle imbalance, a comprehensive treatment program is required to improve the flexion pattern. The effect of the total program was chosen as the focus of this study, rather than the contribution of each individual component (multilevel botulinum toxin A,

physiotherapy, orthoses, and serial casting). Therefore we do not know how much of the effect is specifically contributable to the multilevel botulinum toxin A injections alone, or to the intensive physical therapy, orthosis, or serial casting. The unknown contribution of each of the components and the optimal combination of elements in the treatment program are subjects for future research.

The main focus of this study was on the technical outcomes of gait pattern, muscle length, and spasticity. However, the long-term goal of the multilevel botulinum toxin A and rehabilitation treatment is aimed at improvement on the level of mobility. These results are described in another paper, and it was found that the treatment also has an improved effect on mobility. However, the treatment effects on mobility appear later (12 weeks after injection) than the effect on gait pattern (6 weeks after injection) (results will be presented elsewhere¹⁶).

Conclusion

In this multicenter randomized clinical trial, multilevel botulinum toxin A injections and comprehensive rehabilitation (as opposed to usual care) resulted in a significant improvement in knee extension during gait, muscle length, and spasticity in the injected muscles of children with cerebral palsy whose gait is characterized by a flexed knee pattern. Muscle shortening should not be a contraindication, because the treatment was specifically effective in achieving a significant improvement in muscle length. Although the effect on muscle length was still present after 24 weeks, the effect on gait had disappeared.

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Chapter 5

The combined effect of lower-limb multilevel botulinum toxin type A and comprehensive rehabilitation on mobility in children with cerebral palsy: a randomized clinical trial

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Abstract

Objective: To evaluate the combined effect on mobility of treatment with multilevel botulinum toxin type A (BTX-A) and comprehensive rehabilitation in children with cerebral palsy (CP). **Design:** Randomized clinical trial using a multiple baseline design. The intervention group was treated 6 weeks after randomization. The control group was treated after a longer period of 18 to 30 weeks. Repeated measurements in both groups were continued throughout the process, before and up to 48 weeks after treatment. **Setting:** Four departments of rehabilitation medicine in The Netherlands. **Participants:** Forty-six children with spastic CP (mean age \pm standard deviation, 8.0 ± 2.1 y). **Intervention:** The intervention group ($n=23$) was treated with multilevel BTX-A and comprehensive rehabilitation. Control group subjects ($n=23$) continued with their usual physical therapy (PT) for 18 to 30 weeks, and then also received multilevel BTX-A and comprehensive rehabilitation. **Main Outcome Measures:** The primary outcome measure was the Gross Motor Function Measure (GMFM-66); the secondary measures were problem score and energy cost. **Results:** The treatment effect during the first 24 weeks of follow-up in the intervention group was compared with the effect of usual PT in the control group. Treatment with multilevel BTX-A and comprehensive rehabilitation provided a significantly greater improvement at 12 and 24 weeks in both the GMFM-66 (2.1 points, $P=.02$; and 3.5 points, $P<.01$, respectively) and problem score (1.8 and 1.7 points, $P<.001$, respectively) compared with usual PT. No difference was found in energy cost. Before-after analysis of the total group ($n=46$) showed a significant long-term improvement (48wk) on all outcome measures. **Conclusions:** Treatment with multilevel BTX-A and comprehensive rehabilitation significantly improves mobility as measured by the GMFM-66 and problem score in children with CP.

Introduction

Most children with cerebral palsy (CP) have a deviating gait pattern. One of the typical patterns is characterized by flexion of the knee during midstance¹. These children walk either with a crouch pattern² or with a jump knee pattern² without ever reaching full extension during the midstance. This is often caused by muscle imbalance resulting from a combination of spasticity of flexor muscles, weakness of extensor muscles, and/or coactivation of both flexor and extensor muscles, which may lead to fixed muscle contractures during development. The natural course of development in these children is a further deterioration in the flexion pattern³, which is generally accompanied by a deterioration in mobility⁴. Therefore, treatment at an early stage is indicated to improve knee extension in gait. A comprehensive rehabilitation approach is needed, aimed at both decreasing spasticity and improving muscle strength and length.

Since 1993⁵, injection with botulinum toxin type A (BTX-A) has been used for spasticity management in the lower-leg muscles of children with CP. BTX-A is injected into the muscle, where it produces a local, dose-dependent, and reversible paresis. To improve mobility in children who walk with a flexion pattern, multiple muscle groups should be treated in 1 session (multilevel BTX-A). To optimize the spasticity reduction induced by BTX-A injections, it has been suggested that the muscles should be actively and passively stretched after treatment, based on a comprehensive rehabilitation plan of serial casting and optimal orthotics⁶. Additionally, intensive physical therapy (PT) is indicated to improve muscle strength and length⁷. All these treatment options (casting, orthoses, intensive PT) can be summarized by the denominator of ‘comprehensive rehabilitation.’

Although many randomized studies have evaluated the effect of a single-level BTX-A injection in the gastrocnemius muscle to improve equinus gait⁸⁻¹¹ so far there have been only 3 randomized¹²⁻¹⁴ and 2 nonrandomized^{6,15} studies that exclusively evaluated the effect of multilevel BTX-A injections. Of these studies,

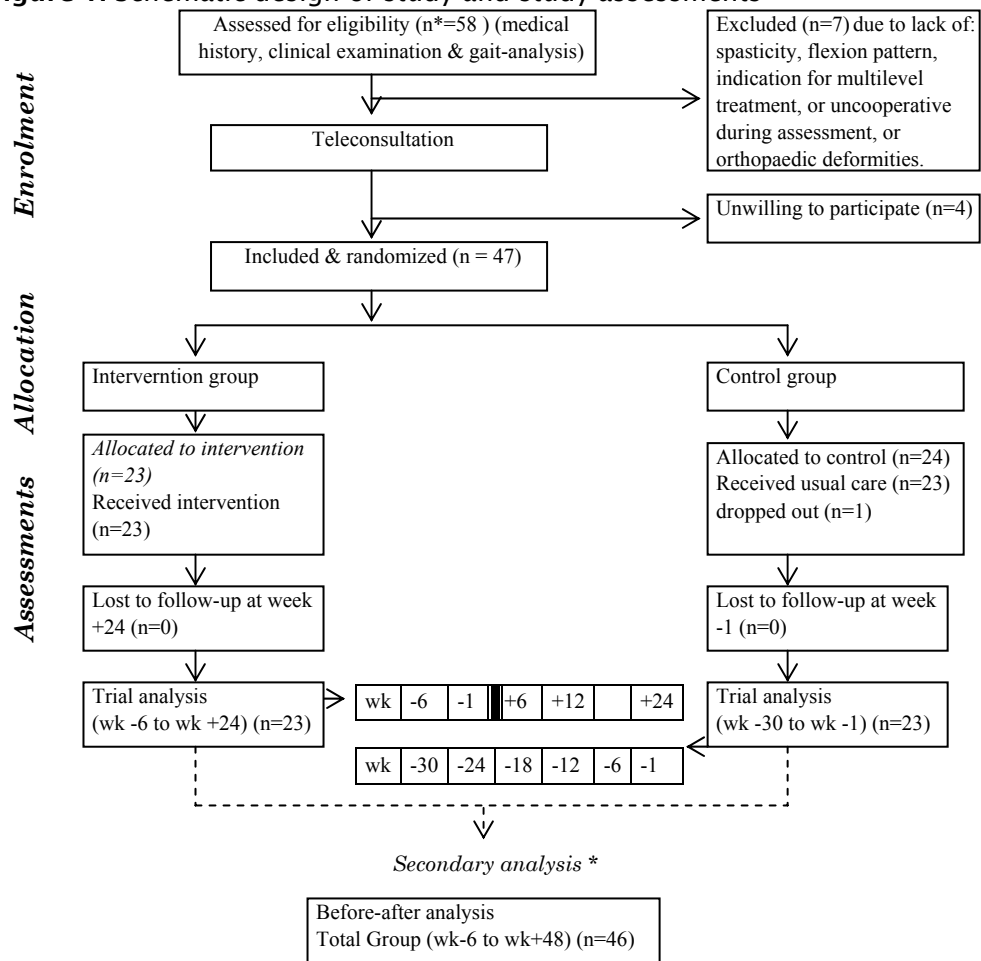
only 1 used a control group that received the usual PT¹³. Moreover, evaluation of the primary outcome in these studies^{6,12,15} was mostly at the level of impairment (range of motion, spasticity, gait kinematics), while the main goal of multilevel BTX-A treatment is at the level of activity, in particular in the domain of mobility¹⁶. Improvement in mobility, in particular, is a more long-term treatment goal. Therefore, our purpose in this randomized study was to measure the effect on mobility of lower-extremity multilevel BTX-A treatment and comprehensive rehabilitation on children with CP who walk with flexed knees in midstance up to 1 year after treatment.

Methods

Study population

Between October 2001 and March 2003, 58 children from 4 Dutch departments of rehabilitation medicine were screened for participation in this trial. The screening included a standardized medical history and clinical examination, and frontal and sagittal plane gait video-recordings with surface electromyography¹⁷. Inclusion was based on the consensus of 4 participating pediatric physiatrists during a teleconsultation session in which the data collected were discussed via high quality audiovisual conferencing¹⁸. The inclusion and exclusion criteria are listed in appendix I.

Forty-seven of the 58 children were found to be eligible and were enrolled. One child, however, withdrew after the first baseline assessment (at the parent's request) and was considered a drop-out. The remaining 46 children participated and were analyzed in the study (fig 1). Table 1 summarizes the patients' personal and treatment characteristics.

Figure 1: Schematic design of study and study assessments

Legend to Figure 1: The duration of baseline for children in the control group varied from 18 to 30 weeks.
*NOTE. Negative values for number of weeks before intervention; positive values for number of weeks after intervention. Thick black line in the intervention group analysis charts demarks multilevel BTX-A injections and comprehensive rehabilitation. *One child in the intervention group and 3 in the control group withdrew from the study after week 24 follow-up. They subsequently underwent myototomy of the gastrocnemius muscle, orthopedic surgery, or selective dorsal rhizotomy, on recommendation of the pediatric physiatrist (JGB).*

Table 1: Personal and treatment characteristics of all participating children and a subgroup of children completing energy cost measurements

<i>Characteristics</i>	<i>Group</i>		<i>Energy Cost Subgroup</i>	
	<i>Intervention (n=23)</i>	<i>Control (n=23)</i>	<i>Intervention (n=11)</i>	<i>Control (n=10)</i>
Sex (boys/girls)	16/7	16/7	6/5	7/3
Diagnosis (unilateral/bilateral)	3/20	1/22	1/10	0/10
GMFCS level (I/II/III/IV)	9/3/10/1	9/4/7/3	6/0/5/ND	3/3/4/ND
Mean age \pm SD (y)	8.1 \pm 2.3	7.1 \pm 2.3	8.3 \pm 2.1	7.2 \pm 1.1
Range	4.2-11.5	4.5-11.0	4.5-10.1	5.7-10.6
Mean weight \pm SD (kg)	26.76 \pm 7.63	25.59 \pm 8.27	27.00 \pm 1.87	24.33 \pm 9.88
Range	15.00-45.00	13.00-44.00	17.00-45.00	13.00-44.00
Mean dosage BTX-A \pm SD (U)	442.83 \pm 132.84	460.00 \pm 101.23	471.36 \pm 92.74	449.00 \pm 98.06
Range	180-710	250-600	340-625	330-570
No. of limbs treated	42	40	20	18
Target muscle groups,* no. of limbs (hst+ps+gc/hst+ps/hst+gc/other)	8/18/9/7	10/14/13/7	4/7/6/3	5/2/9/2
Orthoses (insoles/AFO)	5/17	2/21	3/7	2/8
Casting (yes/no)	6/18	11/12	3/7	6/4

Abbreviations: AFO, ankle-foot orthosis; gc, gastrocnemius; GMFCS, Gross Motor Function Classification System; hst, hamstrings; ND, no data; ps, psoas; SD, standard deviation.

** Most frequently targeted muscles were hamstrings, gastrocnemius, and psoas in varying combinations. Other muscles injected were (alone or in combination) rectus femoris, soleus, adductors, and tibialis posterior.*

Study design and procedure

The children were randomly assigned to 1 of 2 groups: intervention and control (fig 1). An independent statistician (DLK) performed the randomization, using computer-generated random blocks of 4 (all permutations of AABB), stratified per center. The selection, randomization, and measurement procedures are shown in figure 1.

Intervention group

Children in the intervention group (n=23) were treated with multilevel BTX-A injections and comprehensive rehabilitation. This group had 2 assessments during a 6-week baseline period and 4 follow-up measurements, at 6, 12, 24, and 48 weeks after treatment.

Control group

Children in the control group (n=23) continued with their usual PT (low intensity, 1–2 sessions of 30–60min a week, some used orthoses) for a period of 18 to 30 weeks. They were assessed every 6 weeks. After this baseline period, the controls were also treated with multilevel BTX-A injections and comprehensive rehabilitation, with a follow-up at 6, 12, 24, and 48 weeks after treatment.

Multilevel BTX-A injections and comprehensive rehabilitation

During the teleconsultation, a consent treatment plan was formulated for each child regardless of his/her group randomization; the plan included target muscle identification, calculation of injection dose, need for serial casting, and prescription of ankle-foot orthoses (AFOs). Possible target muscles were the psoas, mediolateral hamstrings, hip adductors, rectus femoris, gastrocnemius, soleus, and tibialis posterior. The principles of multilevel surgery were applied in the selection of target muscles, based on the result of gait analysis and clinical examination¹⁹. The injections were given with the subjects under general anesthesia, in at least 2 sites per muscle belly, to a maximum of 50U per site, with a dosage of 4 to 6U/kg of body

weight of BTX-A (Botox) per muscle group. A maximum total dose was set at 25U/kg of body weight for children 5 years or younger, and 30U/kg of body weight for children 6 or more years old, with a maximum recommended dose of 600U. We used a dilution of 50U in 1mL of 0.9% NaCl solution. Injection sites were determined by palpation of the muscle belly, and needle placement was verified by either stretching or electric stimulation of the muscle.

Beginning 1 week after the multilevel BTX-A injections, each child was treated 3 to 5 times a week for 12 weeks by a physiotherapist, according to a standardized treatment protocol. Each session lasted 45 to 60 minutes, and the treatment consisted of stretching the flexor muscles, training to strengthen the extensor muscles, and functional mobility training. If the passive ankle dorsiflexion with extended knee measured during screening was less than 0°, serial casting was initiated 1 to 3 weeks after the injection. Bilateral below-knee walking casts were applied and changed every week until 0° or more of dorsiflexion was achieved. Stiff insoles or AFOs were prescribed to support full knee-extension in terminal stance.

Outcome measures

The primary outcome measure was the Gross Motor Function Measure (GMFM), a standardized observational instrument that requires a child to demonstrate various motor skills, as outlined in the GMFM administration and scoring guidelines. Consequently, it reports a child's actual ability level. In this study, we used the 66-item version of the GMFM (GMFM-66), an internationally recognized valid and reliable objective outcome measure, based on interval scaling²⁰.

Our first secondary outcome measure was the gross energy cost of walking. Energy cost²¹ (in $\text{J} \cdot \text{kg}^{-1} \cdot \text{m}^{-1}$) was determined by measuring oxygen uptake and carbon dioxide production with a portable gas analyzing system^a during a 6-minute walk at a comfortable self-selected speed. Oxygen uptake was converted to joules and expressed relative to walking speed (in m/min) and body mass (in kilograms)²¹. Mean steady-state values during the last 60 seconds were used for analysis. This test was performed in a subgroup (n=24) in 1 center only.

Another secondary outcome measure was a parent self-reported problem score, which recorded the 3 main problems related to lower-extremity mobility tasks experienced by their child. We used a semi-structured interview method and a standardized set of examples. Each problem was rated by the parent in terms of difficulty of performance on an 11-point scale (0 [no problem] to 10 [major problem]).

The GMFM-66 and energy costs were assessed during all baseline and follow-up measurements in both groups. At baseline, the problem score was assessed once in the intervention group and twice in the control group and at all follow-up visits. The children were assessed and treated in their own recruitment center. It was not possible to blind the observers for treatment group—the groups were transparent because of their different number of assessments. All observers were certified to administer the GMFM-66 and were fully trained to perform all the assessments. Moreover, to reduce testing bias in the subjective prediction of change in one of the outcome measures, the observers never reviewed any previous test values.

Based on the GMFM-66, this study had a power of 71% (47 subjects were initially enrolled) to detect a mean change of 1.6 points between the groups, with a 2.2-point standard deviation (SD) on GMFM-66 scores. This mean change of 1.6 points on the GMFM-66 could be considered a clinically meaningful change of motor function²².

Approval for the study was obtained from the Medical Ethics Committee of the VU University Medical Center in Amsterdam and full written informed consent was obtained from all parents and children 12 years of age or older before enrolment.

Statistical analysis

Group characteristics were tested for differences with the Student *t* test (continuous data) or the chi-square test (dichotomous or ordinal data). We used 2 types of analysis to study the treatment effect. The strongest level of evidence was given by the trial analysis, in which the effect in the intervention group (–6wk before to 24wk after treatment) was compared with the usual PT effect in the control group (–30wk to –1wk before treatment). Additionally, using secondary before-after analysis, the long-term effect at 48 weeks after treatment was compared with before-treatment (–6 and –1wk) values. For these analyses, the full follow-up term of the total population (intervention group plus control group) was used. To identify characteristics of the children who might have responded differently to treatment, subgroup analysis were performed for the level of functioning classified with the Gross Motor Function Classification System (GMFCS)²³ and age (<7y, ≥7y), also in the total population.

All differences in effect were analyzed in a linear mixed-model analysis^{24, b} which estimated the treatment effect on the different outcome measures while adjusting for dependency of repeated observations in each subject. The factor ‘center’ was considered in all statistical analyses. An independent statistician (DLK) and the principal investigator (VAS) performed all analyses. The level of statistical significance was set at *P* less than .05, which was adjusted in the subgroup analysis through Bonferroni adjustment. All *P* values were 2-sided.

Results

The mean baseline period from the first baseline assessment until the time of treatment ± SD was 5.8±1.0 weeks in the intervention group (range, 4–8wk) and

23.6±6.8 weeks in the control group (range, 10–35wk). The groups did not differ with regard to personal characteristics (see table 1).

Each patient was treated with multilevel BTX-A in at least 1 limb. A mean dose of 18.01±4.74U/kg of body weight was injected, ranging from 5.63 to 27.14U/kg of body weight.

Trial analysis

For all outcome measures the estimated mean difference between the 2 groups in change from initial baseline and the 95% confidence intervals (CIs) are shown in table 2 (see Trial Analysis).

A significant treatment effect on the GMFM-66 was found 12 and 24 weeks after treatment in the intervention group (fig 2A). On the energy cost test, 2 children with GMFCS level IV (control group) did not reach a steady state of oxygen uptake during walking. Another child was afraid of the mask, which made testing impossible (control group). These 3 were excluded from the analysis. Group characteristics of the remaining 21 children are presented in table 1. No significant treatment effect was found in energy cost (see fig 2B). On the problem score, the parents reported a total of 40 different problems involving balance (unaided standing, unaided walking, getting on or off a bicycle), falling or tripping, walking (walking longer distances, walking indoors or outdoors, walking with bare feet, climbing stairs, walking on uneven surfaces, walking in a supermarket), transfers (getting in or out of a car, rising from the ground unaided), running, and playing (jumping a rope, kicking a ball). A significant treatment effect on problem score was found in the intervention group 12 and 24 weeks after treatment (see fig 2C).

Before-after analysis: long-term effect

The last values assessed in both groups before treatment (mean of –6 and –1 week for the GMFM-66 and energy cost, –1 week for the problem score, respectively) were used as baseline values to compare the long-term effect (48 wk) for the total group (n=46). These are presented in table 2 (see Baseline Values). No significant

Table 2: Three types of results: last baseline values for the intervention group (n=23) and control group (n=23); trial analysis of estimated mean difference between the 2 groups in change from initial baseline; and before-after analysis for estimated mean long-term change from baseline for the total group (n=46)

Outcome	Baseline Values*		Trial Analysis		Before-After Analysis	
	Intervention Group	Control Group	Estimated Mean Difference in Change†	P‡	Estimated Mean Long-Term Change	P‡
<i>GMFM-66 (0-100)</i>						
Baseline	67.91 ± 15.39	65.90 ± 11.37				
Week +6§			-0.77 (-3.07 to 1.52)	.50	-0.83 (-1.93 to 0.26)	.13
Week +12			2.07 (0.31 to 3.83)	.02	1.43 (0.69 to 2.17)	<.001
Week +24			3.48 (1.34 to 5.61)	.002	2.07 (0.96 to 3.18)	<.001
Week +48					2.26 (1.29 to 3.22)	<.001
<i>Energy cost (J·kg⁻¹·m⁻¹) </i>						
Baseline	11.61 ± 6.57	10.77 ± 3.13				
Week +6			-0.88 (-2.75 to 0.99)	.35	0.26 (-0.46 to 0.98)	.46
Week +12			0.50 (-1.37 to 2.38)	.59	-0.07 (-1.40 to 1.26)	.91
Week +24			0.31 (-1.58 to 2.21)	.74	-0.90 (-1.59 to -0.20)	.01
Week +48					-1.78 (-2.64 to -0.92)	<.001
<i>Problem score (0-10)</i>						
Baseline	7.81 ± 1.66	8.25 ± 1.51				
Week +6			-0.70 (-1.44 to 0.04)	.07	-0.85 (-1.53 to -0.17)	.02
Week +12			-1.78 (-2.62 to -0.93)	<.001	-1.83 (-2.54 to -1.11)	<.001
Week +24			-1.65 (-2.81 to -0.48)	<.001	-1.90 (-2.54 to -1.27)	<.001
Week +48					-1.40 (-2.04 to -0.76)	<.001

NOTE. Values are mean ± SD or mean (95% CI). For GMFM-66 a positive value indicates improvement; for energy cost and problem score a negative value indicates improvement. * Mean of -6 and -1 week for the GMFM-66 and energy cost, and -1 week for the problem score, respectively.

† Corrected for baseline differences. ‡ P values with linear mixed-model analysis, models are adjusted for center.

§ The positive values indicate the number of weeks after intervention.|| Energy cost only presented for subgroup; in the before-after analysis 1 additional patient was left out of the analysis.

differences were found. The results of these before-after analyses are also presented in table 2 (see Before-after Analysis), showing estimated mean changes from this baseline for the total group and 95% CIs at 48 weeks after treatment. Significant improvements were found in all outcome measures, GMFM-66, energy cost, and problem score, at 48 weeks after treatment.

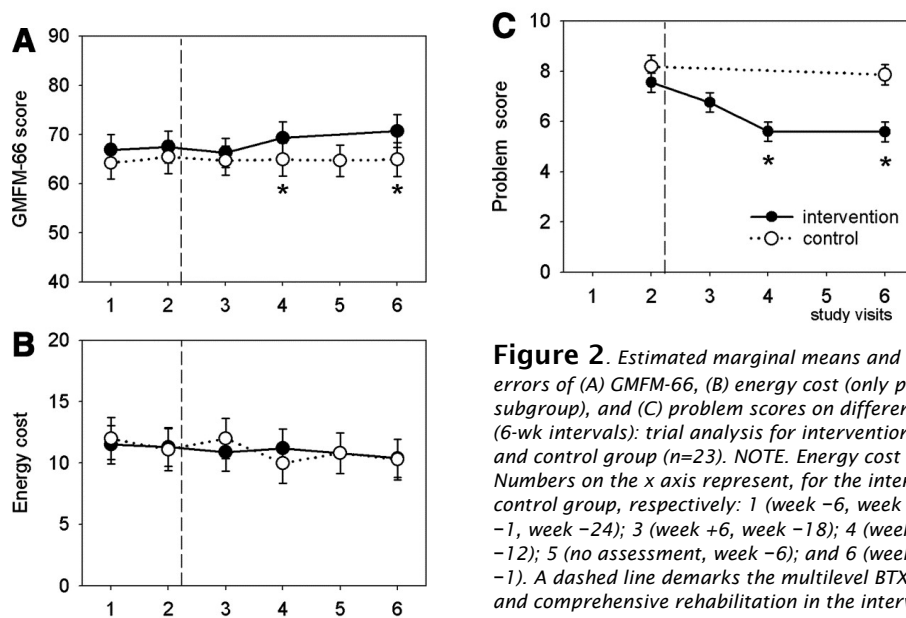


Figure 2. Estimated marginal means and standard errors of (A) GMFM-66, (B) energy cost (only presented for subgroup), and (C) problem scores on different study visits (6-wk intervals): trial analysis for intervention group (n=23) and control group (n=23). NOTE. Energy cost is in J·kg⁻¹·m⁻¹. Numbers on the x axis represent, for the intervention and control group, respectively: 1 (week -6, week -30); 2 (week -1, week -24); 3 (week +6, week -18); 4 (week +12, week -12); 5 (no assessment, week -6); and 6 (week +24, week -1). A dashed line demarks the multilevel BTX-A injections and comprehensive rehabilitation in the intervention group. *Significant difference in change between the intervention group and the control group, corrected for baseline differences (P<.05).

Before-after analysis: subgroup effect

Subgroup analysis showed that the energy cost in children with GMFCS level III was improved significantly more 48 weeks after treatment, compared with children with GMFCS levels I and II (see fig 3B). For the other outcome measures, no significant differences in effects were found for different GMFCS levels (see figs 3A, C) or age subgroups (results not presented).

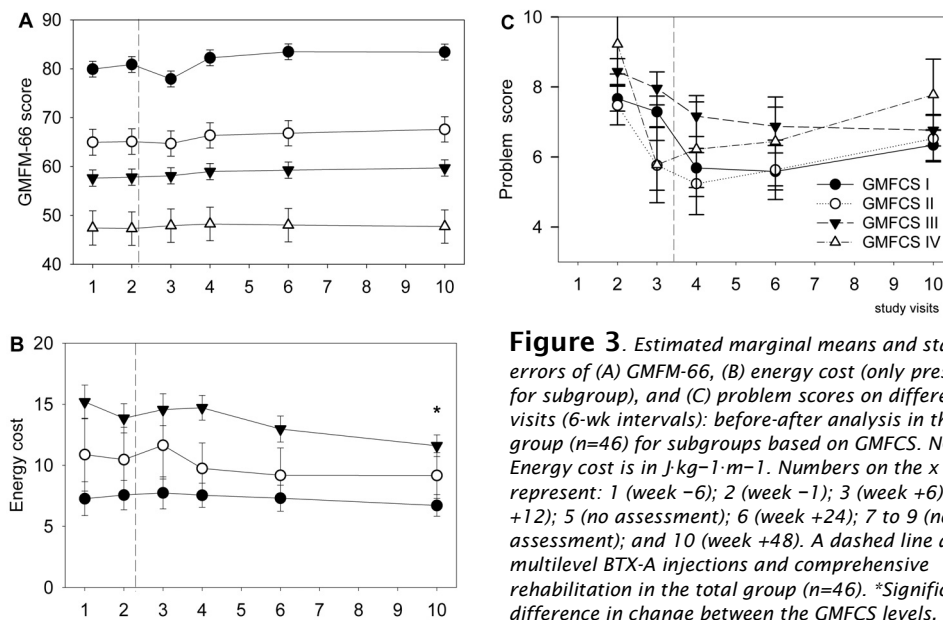


Figure 3. Estimated marginal means and standard errors of (A) GMFM-66, (B) energy cost (only presented for subgroup), and (C) problem scores on different study visits (6-wk intervals): before-after analysis in the total group (n=46) for subgroups based on GMFCS. NOTE. Energy cost is in J·kg⁻¹·m⁻¹. Numbers on the x axis represent: 1 (week -6); 2 (week -1); 3 (week +6); 4 (week +12); 5 (no assessment); 6 (week +24); 7 to 9 (no assessment); and 10 (week +48). A dashed line demarks multilevel BTX-A injections and comprehensive rehabilitation in the total group (n=46). *Significant difference in change between the GMFCS levels, corrected for baseline differences (P<.05).

Discussion

In this randomized clinical trial, we evaluated the effect of treatment with multilevel BTX-A and comprehensive rehabilitation on the mobility of children with CP who were walking with flexion of the knee in midstance.

In the trial analysis, we found that multilevel BTX-A given in combination with comprehensive rehabilitation significantly improved gross motor function. In addition, parents of the patients reported a significant improvement in the perceived difficulty of individually selected mobility tasks. We found no evidence, however, of a treatment effect on the energy cost of walking.

The improvement on the GMFM-66 (3.5 points) found at 24 weeks after treatment was a small, but significant, treatment effect. In the literature, the reported change over 1 year in children more than 5 years of age who received usual care was less than 1 point on the GMFM-66²⁰. Recently, it was shown that a change score of 1.6 points is clinically meaningful, and a change score of 3.7 points discriminates moderate or no improvement from a great improvement²². Relative to these changes, we believe that our results indicate a clinically meaningful improvement in gross motor function. The secondary before-after analysis also indicates that long-term effects (>1y) on gross motor function can be expected, but this needs to be confirmed in a randomized controlled trial.

One other randomized study¹³ also evaluated multilevel BTX-A with the GMFM and found no significant difference between the multilevel BTX-A group and the group continuing with regular (nonintensive) PT. This study had a crossover design that evaluated the effects over a period of 6 months. Because we showed that an effect 1 year after treatment can still be expected, a 6-month period might have been too short. Other randomized studies⁸⁻¹¹ failed to show any significant treatment effect of single level BTX-A injections without intensified PT on the GMFM in children walking with equinus. Our results might suggest that the combined effect of multilevel BTX-A treatment and comprehensive rehabilitation

could be more effective in improving gross motor function than multilevel BTX-A alone. This is speculative, however, and can only be confirmed in a randomized trial that compares multilevel BTX-A alone to multilevel BTX-A and comprehensive rehabilitation.

Some authors^{14,25} advise that multilevel BTX-A injections should only be given to children up to 7 years old. The results of our subgroup analysis, however, showed no difference in treatment effects between children of a minimum age of 7 and younger children.

Although the children in this study were selected on the basis of an energy-inefficient gait pattern of knee flexion²⁶, we found no treatment effect on energy cost in the trial analysis. The small number of patients available for energy cost analysis might have influenced this. Nevertheless, the estimated mean changes at these different follow-ups were all less than 10%, which also does not seem clinically relevant. Secondary before-after analysis showed an improvement of more than 10% at 48 weeks, which was significant. Without the use of a control group, however, the study power of this analysis was 56%, which therefore limits the interpretation of these findings. In the long-term, children who used walking aids (GMFCS level III) improved significantly more than did children walking without aids (GMFCS levels I and II). As shown in figure 2B, this may be because children with GMFCS III, with a baseline energy cost twice as high as children with GMFCS level I, have more scope to improve. Children in the latter group seem to be nonresponsive to change in energy cost because their energy cost is already low, although it is higher than that of healthy children.

A significant treatment effect was seen on the problem score at 12 and 24 weeks. Compared with other reports, where the clinically relevant change was set at 10% of the total range of the scale⁹, our results indicate a clinically relevant change. Problems frequently mentioned by parents were (1) falling and tripping during walking, (2) limited duration of walking, and (3) problems with balance. Although the problem score is self-developed and not validated, it may reveal benefits

associated with the parents' subjective experience of improvement in a child's mobility.

We also found a long-term improvement on the problem score at 48 weeks after treatment. All children continued with their usual PT after the period of intensive PT (12wk), with the same intensity as before the multilevel BTX-A injections; only 1 child was re-treated with a BTX-A injection and only in the rectus femoris muscle (at 30wk after treatment, without comprehensive rehabilitation), and none had serial casting again. Therefore, the long-term effects found in this study on all outcome measures might suggest that combined treatment of multilevel BTX-A and comprehensive rehabilitation can result in an overall long-term improvement in mobility, even 1 year after treatment. This should be confirmed in a randomized controlled study, however.

Study limitations

General shortcomings of this study were the use of multiple assessors (multicenter trial), the lack of assessor blinding, and the varying duration of baseline in the control group. To standardize the treatment and assessment methods, training sessions were organized before the study. All assessors also attended the GMFM course and passed its criterion test. A varying baseline for the control group was necessary because we had to strike a balance between what was scientifically desirable, practically obtainable, and clinically needed: if treatment was planned during the holidays, or a child complained of pain, the physician decided to schedule multilevel BTX-A treatment earlier. A period of 18 weeks was therefore set as a minimum in the control group. Using the linear mixed-model analysis, we adjusted for any missing visits during the study²⁴. It is not clear whether the varying baseline influenced our results. Although all control children were scheduled to receive multilevel BTX-A treatment and comprehensive rehabilitation, we found stable baseline values for all outcome measures. If the baseline period had been 30 weeks for all children (including the ones who complained of pain), it would seem reasonable to expect stable values as well, or

even slightly deteriorating baseline values rather than improved ones, leading to similar or even greater treatment effects.

We selected children with a flexion gait pattern for treatment. This pattern is caused by an imbalance of flexor and extensor muscle activity, which necessitated the application of a comprehensive treatment program. We chose the effect of the total program as the subject for this study, rather than the contribution of each component (multilevel BTX-A, intensive PT, serial casting and orthoses); therefore, we do not know, for example, how much of the effect is specifically contributable to the multilevel BTX-A injections alone, or to the intensive PT. Because the optimal combination of these factors is not known, the contribution of each of the components of the treatment program must be assessed in future research.

The main focus of this study was on the level of mobility, because this is the main and final goal of the BTX-A and rehabilitation treatment. Effect of the treatment on technical outcome measures was outside the scope of this study. We are currently preparing a second report that will discuss the effect of multilevel BTX-A and comprehensive rehabilitation on video-based gait analysis, range of motion as a measure of muscle length, and spasticity.

Conclusions

Combined treatment with multilevel BTX-A and comprehensive rehabilitation is an effective treatment modality that leads to clinically relevant improvements in gross motor function and self-reported mobility tasks in children who walk with flexion of the knees. We found no accompanying change in energy cost of walking.

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Supplier

^a VmaxST, version 1.0; SensorMedics BV, PO Box 299, 3720 AG Bilthoven, The Netherlands.

^b Version 11.5; SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.

Appendix I: Inclusion and Exclusion Criteria

<i>Inclusion criteria</i>	<i>Exclusion criteria</i>
Diagnosis of CP	BTX-A treatment in lower extremities within 16 weeks before inclusion
Spastic hemiplegia or diplegia (according to Hagberg ²⁷)	Orthopedic surgery 24 weeks before inclusion
Age between 4 and 12y	Contraindication for BTX-A
Spasticity* in 2 or more lower-extremity muscle groups interfering with mobility	Contraindication for general anesthesia
GMFCS levels I to IV	Orthopedic deformities that have a bad influence on walking
Gait characterized by persistent flexion of the knee ($\geq 10^\circ$) in mid-stance (barefoot or with AFOs/shoes)	- (Sub)luxation of the hip with an MI $> 50^\circ$
Two or more muscle groups in 1 limb needing BTX-A injection	- Hip endorotation contracture $> 15^\circ$
Ability to carry out instructions	- Flexion contracture of knee $> 15^\circ$
Adequate knowledge of the Dutch language	Severe fixed contractures:
	Age $< 8y$
	- Ankle plantarflexion with knee extended $> 20^\circ$ †
	- Popliteal angle $> 90^\circ$
	Age $\geq 8y$
	- Ankle plantarflexion with knee extended $> 15^\circ$ †
	- Popliteal angle $> 80^\circ$
	Presence of ataxia or dyskinesia
	Other problems that have a negative influence on walking

Abbreviations: AFOs, ankle-foot orthoses, GMFCS, Gross Motor Function Classification System; MI, migration index²⁸.

** Spasticity was defined during clinical examination as the occurrence of a 'catch' (sudden increase in muscle tone) somewhere before the end of the range of motion in response to a fast passive stretch (in hamstrings, adductor, rectus femoris, gastrocnemius, and soleus muscles).*

† From neutral.

Chapter 6

Can we identify predictors of multilevel botulinum toxin type A injections and comprehensive rehabilitation in children with cerebral palsy?

Submitted as:

Scholtes VA, Dallmeijer AJ, Becher JG. Can we identify predictors of multilevel botulinum toxin type A injections and comprehensive rehabilitation in children with cerebral palsy?

Abstract

This study evaluates whether the in literature reported potential predictors can predict the outcome of multilevel BTX-A injections in children who walk with a flexed knee. Forty-six children with spastic CP, aged between 4 and 12 years, participated in this study. Multiple linear regression analysis was applied to study the associations between 11 predictors and 2 different outcome measures (the Gross Motor Function Measure [GMFM66] and knee angle at midstance) at 6, 12, 24 and 48 weeks of follow-up. Each model was adjusted for the outcome score or value at baseline.

Only age was found positively associated with change in the GMFM66 at 12 weeks follow-up, and only ankle angle at midstance was found positively associated with change in knee angle at midstance at 48 weeks follow-up. Of these, only the former association was found to be clinically relevant. Furthermore, the baseline GMFM66 score was negatively associated with change in GMFM66 at 6 weeks but not at the other follow-up measurements. The baseline knee angle at midstance was negatively associated with change in knee angle at midstance at 6 and 48 weeks follow-up, but not at 24 weeks.

This study shows that the majority of potential predictors do not predict the outcome of multilevel BTX-A injections and comprehensive rehabilitation in children who walk with a flexed knee pattern. The only relevant significant predictor for favourable responses in this patient group, with regard to gross motor function, is older age.

Introduction

In children with cerebral palsy (CP), gait and mobility problems are very common^{1, 2}. In recent years, several studies have shown the ameliorating effect of botulinum toxin A (BTX-A) injections in gait and mobility after injection of the M. Triceps Surae in children walking in equinus³⁻⁵. Our study group recently found in a randomised clinical trial that, in children who walk with a flexed knee pattern, multilevel BTX-A injections (different muscles acting over different joints injected in one session) combined with comprehensive rehabilitation leads to a significant improvement in knee extension at midstance after 6 weeks (increase of 7°, $p < 0.01$)⁶, and to a significant improvement in gross motor function, measured with the Gross Motor Function Measure (GMFM66), after 12 weeks (increase of 2.1 points, $p = 0.02$), which continued until 24 weeks (increase of 3.5 points, $p < 0.01$)⁷.

However, not all treated children are found to be response to BTX-A treatment⁸. Various factors are suggested to be predictive of a good response. For patients with equinus gait, these are often described as: young age, mild to moderate severity of motor involvement (classified according to the Gross Motor Function Classification System [GMFCS]⁹) and the absence of fixed contractures (e.g. no limited range of motion [ROM])^{10, 11}. Although the scientific evidence for these potential predictors is only limited, clinicians often use these as indication criteria, to serve as a guiding principle for the choice of treatment¹¹⁻¹³. As a consequence, children who do not meet these criteria (e.g. older children, with less severe involvement, and fixed contracture) might therefore *not* be selected for treatment.

Recently, two studies focused on the evaluation of predictors of a good response on BTX-A treatment in children with CP^{14, 15}. Besides the earlier suggested factors (age, severity of motor involvement, ROM), they also evaluated gender, spasticity (rated on the Ashworth Scale¹⁶), localisation of the motor disorder, level of motor function (measured with the GMFM¹⁷). It was found that different factors were

related to different types of outcome: spasticity, level of motor function, and ambulation status were related to the parent's experienced improvement¹⁴; age was related to the outcome on the GMFM¹⁵; and localisation was related to outcome on selective motor control¹⁵ and gait pattern¹⁵. This might indicate that none of these factors can be regarded as a true predictor. Furthermore, it is noteworthy that severity of motor involvement and ROM were not found to be predictive for any of the outcome measures^{14, 15}, despite their suggested potentiality¹⁰.

The former two studies only included children walking with equinus. Since these children may differ in various characteristics from children walking with flexed knee gait, it is possible that different factors might be predictive of a good response on multilevel BTX-A treatment. However, no study has yet identified possible predictors in children who walk with a flexed knee pattern who were treated with multilevel BTX-A injections to improve gross motor function and gait pattern.

The aim of the present study was therefore to describe the number of responders to multilevel BTX-A treatment and to evaluate whether the in literature suggested factors are predictive of a favourable outcome on gross motor function and knee angle at midstance after multilevel BTX-A treatment, in children walking with flexed knee gait.

Methods

Participants

From October 2001 to March 2003, 58 children were screened for this multicenter trial in four Dutch departments of rehabilitation medicine, and 46 children were included in the study. The main inclusion criteria were: aged between 4 and 12 years, ability to walk with/without a walking aid (GMFCS⁹ I-IV), gait characterized by persistent flexion of the knee ($\geq 10^\circ$) in midstance. Children with

severe contractures were excluded (see Scholtes et al.^{6, 7} for exact inclusion and exclusion criteria).

Design

All were participants in a randomised clinical trial to evaluate the effect of multilevel BTX-A and comprehensive rehabilitation in children with CP. All 46 children were treated with multilevel BTX-A injections (BOTOX®, Allergan, Nieuwegein, the Netherlands) under general anesthesia, followed by comprehensive rehabilitation (standardized physical therapy; serial casting; and/or new orthosis) (see Scholtes et al.^{6, 7} for a more detailed description of the study).

The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam. Full written informed consent was obtained from all parents, and also from 12 year-old children, prior to enrolment.

Measurements

Outcome measures

The two outcome measures were gross motor function (measured with the GMFM¹⁷) and the knee angle at midstance during gait. The GMFM was assessed by trained and certified examiners at 6 weeks before treatment and at 6, 12, 24 and 48 weeks after treatment (barefoot, without a walking aid). We used the 66 item version of the GMFM (GMFM66), which is a standardized observational instrument based on interval scaling¹⁷, that requires the child to demonstrate various motor skills as outlined in the GMFM administration and scoring guidelines.

2-D gait analysis was performed with the child walking barefoot (with or without a walking aid) on a 10 metre pathway at 6 weeks before treatment and at 6, 24 and

48 weeks after treatment. The videorecordings were randomly assessed by a blinded research assistant, from which the sagittal knee angles at midstance (in degrees) were measured using a digital screen goniometer. The mean (right and left) knee angle at midstance was used as the outcome measure.

Predictors

All variables that have been described as potential predictors in literature were included (see Table 1). The variables were derived from medical history (personal and disease characteristics), physical examination (motor impairments) gait analysis (motor impairments), and GMFM66 assessment (motor function) that was taken from each patient at baseline.

Statistics

All analysis were performed in SPSS (11.5) for Windows. To describe the number of responders to the treatment on the two different outcome measures, three categories of responders were used: 'good' (GMFM: $\geq +1.6$ points¹⁸; knee angle: $\geq +5^\circ$ [towards extension]), 'non' (GMFM: $>+1.6$ and $< +1.6$ points; knee angle: $> +5^\circ$ and $< +5^\circ$) and 'bad' (GMFM: $\leq +1.6$ points; knee angle: $\leq +5^\circ$ [towards flexion]). For this purpose, the individual changes in the GMFM66 and the knee angle at midstance were calculated for each patient by subtracting the baseline value from the value at each follow-up measurement. For both outcomes, a positive change indicates a favourable response.

Linear regression analysis was then used to identify the potential predictors for outcome on the GMFM66 and knee angle at midstance. First, each of the potential predictors presented in Table 1 was included in the model, one by one, for each outcome measure. All models were adjusted for their corresponding score at

baseline (i.e. GMFM66 score, or knee angle at midstance). Then, only the potential predictors that showed a univariate association with $p < 0.10$ were selected and entered simultaneously in a final linear (multivariate) regression analysis. Separate models were built for the different follow-up assessments: 6 weeks, 12 weeks, 24 weeks, and 48 weeks.

Results

Study population and baseline characteristics

Four children withdrew from the study after the 24th week of follow-up, and underwent myotendotomy of the gastrocnemius muscle, orthopedic surgery or selective dorsal rhizotomy on the recommendation of the pediatric physiatrist (JB). Therefore, at week 48, only 42 children were assessed. The personal and treatment characteristics of the children are summarised in Table 1.

The mean ROM of the hamstrings (64.1°) and gastrocnemius (1.6°) muscle indicate that these muscles are shortened in this study population, compared to the normal ROM¹⁹. There was spasticity in the hamstrings and the gastrocnemius muscles. The children walked with a mean knee flexion at midstance of 24.2° (SD 12.4), and with a mean ankle flexion at midstance of -5.6° (SD 22.5), which indicates mild plantar flexion. The high standard deviation of the ankle flexion at midstance indicates that there were also children who walked with ankle dorsiflexion.

Table 1: Characteristics of the study population (n = 46)

<i>Characteristics</i>		<i>Predictors</i>
<i>Medical history: personal and disease characteristics</i>		
Gender (boy: girl)	32:14	★
Age, year	8.0 (2.1)	★
Weight, kg	26.2 (7.9)	
Severity of motor involvement according to the GMFCS (I: II: III: IV)	18:7:17:4	★*
Localisation of the motor disorder (unilateral: bilateral)	4:42	★
<i>Treatment</i>		
Dosage BTX-A, U/kg	18.0 (4.7)	
Serial casting, n	17	
Orthoses n	45	
<i>Baseline values: motor impairments and motor function</i>		★
Range of motion (ROM)† °	hamstrings	64.1 (13.5) ★
	gastrocnemius	1.6 (8.2) ★
Spasticity† °	hamstrings	78.0 (17.4) ★
	gastrocnemius	-16.6 (12.3) ★
Gait kinematics‡ °	knee angle at midstance	-24.2 (12.4) ★
	ankle angle at midstance	-5.6 (22.5) ★
Functional muscle strength§	squat test (unable:able)	12:32 ★
Level of motor function	GMFM66	66.8 (13.4) ★

Data are mean (SD); BTX-A = botulinum toxin type A. *Dummies were used for levels I to IV, the reference category was GMFCS I; †ROM and spasticity were assessed with the (relaxed) child lying on an examination couch, with head in midline and arms in an anatomically neutral position. Spasticity was defined as the occurrence of a 'catch' (sudden increase in muscle tone) somewhere before the end of the range of motion in response to a fast passive stretch. ‡Means of right and left leg. §Measured with the squat-test: the child stands in front of the observer, hands may be held for balance, with both feet a shoulder width apart; the child is asked to squat down towards the floor and subsequently stand up again (sitting or touching the floor with buttocks is not allowed) 8 times, or until the child is fatigued (score: unable [<8x] or able [≥ 8x]).

Good, non and bad responders

Table 2 describes the different categories of responders on the GMFM66 and the knee angle at midstance and their mean change at the different follow-up measurements. The GMFM66 was not assessed in one child at 6 weeks after treatment, and gait-analysis was not performed for one child at 48 weeks after treatment. The results show that on both outcome measures,

Table 2: Descriptives of good, non and bad responders on GMFM66 and knee angle at midstance at different follow-up measurements after treatment (in numbers and percentages)

		<i>GMFM66</i>			<i>knee angle at midstance (°)</i>		
		<i>n (%)</i>	<i>mean Δ (SD)</i>	<i>range Δ</i>	<i>n (%)</i>	<i>mean Δ (SD)</i>	<i>range Δ</i>
<i>Week 6</i>	<i>good</i>	10 (22)	3.0 (1.3)	1.6 : 5.6	26 (57)	11.7 (5.7)	5.0 : 25.0
	<i>non</i>	23 (50)	0.1 (0.8)	-1.59 : 1.35	18 (39)	0.9 (3.1)	-4.0 : 4.5
	<i>bad</i>	12 (28)	-5.7 (3.4)	-11.33 : -1.83	2 (3)	-17.0 (2.1)	-18.5 : -15.5
<i>Week 12</i>	<i>good</i>	21 (46)	3.5 (1.7)	1.6 : 8.0	n.a.	n.a.	n.a.
	<i>non</i>	22 (48)	0.1 (1.0)	-1.6 : 1.6	n.a.	n.a.	n.a.
	<i>bad</i>	3 (6)	-3.4 (1.7)	-5.3 : -2.2	n.a.	n.a.	n.a.
<i>Week 24</i>	<i>good</i>	22 (48)	4.9 (3.5)	1.6 : 14.5	15 (33)	10.0 (4.5)	5.0 : 21.5
	<i>non</i>	21 (46)	-0.1 (1.0)	-1.6 : 1.2	21 (47)	0.6 (2.2)	-2.5 : 4.5
	<i>bad</i>	3 (7)	-3.3 (1.5)	-5.0 : -2.2	9 (20)	-8.2 (4.2)	-18.5 : -5.5
<i>Week 48</i>	<i>good</i>	23 (55)	4.5 (2.8)	1.8 : 14.5	8 (19)	12.2 (4.9)	5.0 : 20.5
	<i>non</i>	16 (38)	0.1 (1.0)	-1.6 : 1.6	30 (71)	0.0 (3.0)	-4.5 : 4.5
	<i>bad</i>	3 (7)	-2.2 (0.7)	-3.0 : -1.6	4 (10)	-16.8 (5.8)	-24.0 : -12.0

Δ=change from baseline; n.a. = no assessment

there were children who improved, but also children who remained stable, or who even deteriorated. The greatest good response on the knee angle at midstance was found at 6 weeks after treatment (good responders: 57%). The effect decreased to 19% in good responders after 48 weeks. In contrast, only 22% of the children were good responders on the GMFM66 after 6 weeks; this increased to 46% after 12 weeks, and continued to increase up to 55% after 48 weeks. Remarkable is the overall large group of non-responders on both outcomes, which varied around 50% at most follow-up measurements.

Predictors of GMFM66

Table 3 shows the results of the final (multiple) regression analysis. At 12 weeks after treatment, only age was positively associated with change in GMFM66 (regression coefficient 0.38), indicating that the treatment had a better effect on older children: one year increase in age results in 0.38 point increase in GMFM66. The baseline score showed a significant negative association (regression coefficient -0.10) with the short term (6 weeks) change in GMFM66, indicating that children with a lower level of motor function showed more improvement on the GMFM66. No significant predictors were found for 24 and 48 weeks after treatment. The multiple regression analysis explained 21% and 19% of the variance of change in GMFM66 score at 6 and 12 weeks, respectively.

Predictors of knee angle at midstance

Table 3 also shows the results of the final (multiple) regression analysis. The baseline knee angle at midstance showed a significant negative association with the change in the angle at midstance at 6 weeks (regression coefficient -0.26) and at 48 weeks (regression coefficient -0.32), indicating that children with more knee flexion at baseline showed more improvement on the knee angle at midstance. At 48 weeks, only the ankle angle at midstance was positively associated in such a way that the treatment had a better

effect in children who walk with more ankle (dorsi)flexion at midstance: an increase of 1° in ankle (dorsi)flexion resulted in 0.21° increase in knee angle at midstance. The multiple regression analysis at week 48 explained 36% of the variance of change in the knee angle at midstance.

Table 3: Results of (multiple) regression analysis* on change in GMFM66: (multiple) regression coefficients (B) and 95% confidence interval for each predictor at different follow-up measurements

<i>Dependent variable</i>	<i>Follow up</i>	<i>B</i>	<i>Predictor</i>	<i>95% CI</i>	<i>p-value</i>	<i>R²</i>
Δ GMFM66	week 6	5.53	Intercept	0.34 : 10.72	0.037	21.2%
		-0.10	GMFM66 score at baseline	-0.17 : -0.02	0.013	
		0.12	ROM gastrocnemius	-0.01 : 0.24	0.063	
	week 12	-2.71	Intercept	-6.61 : 1.18	0.167	19.2%
		0.02	GMFM66 score at baseline	-0.04 : 0.07	0.510	
		0.38	Age	0.02 : 0.74	0.041	
		0.07	ROM gastrocnemius	-0.01 : 0.16	0.097	
	week 24	-2.89	Intercept	-8.45 : 2.67	0.300	7.1%
		0.07	GMFM66 score at baseline	-0.01 : 0.16	0.073	
	week 48	-1.59	Intercept	-6.61 : 3.43	0.526	6.2%
		0.06	GMFM66 score at baseline	-0.01 : 0.13	0.111	

B=regression parameter; CI = Confidence Interval; Δ = change from baseline; R^2 = R-square (the proportion of explained total variance explained by the final model)

** only those predictors that were correlated significantly ($p < 0.05$) or showed a trend for correlation ($p < 0.10$) with the mean change in GMFM66 (corrected for GMFM66 score at baseline) are included in the model*

Table 4: Results of (multiple) regression analysis* on change in sagittal knee angle at midstance: (multiple) regression coefficients (B) and 95% confidence interval for each predictor at different follow-up measurement points

<i>Dependent variable</i>	<i>Follow up</i>	<i>B</i>	<i>Predictor</i>	<i>95% CI</i>	<i>p-value</i>	<i>R²</i>
Δ knee angle at midstance	week 6	0.04	Intercept	-5.27 : 5.36	0.987	13.5%
		-0.26	knee angle at midstance at baseline	-0.45 : -0.06	0.012	
	week 24	-0.27	Intercept	-5.21 : 4.67	0.913	2.4%
		-0.09	knee angle at midstance at baseline	-0.27 : 0.09	0.307	
	week 48	-5.50	Intercept	-10.82 : -0.18	0.043	36.1%
		-0.32	knee angle at midstance at baseline	-0.52 : -0.12	0.003	
		0.21	ankle angle at midstance at baseline	0.00 : 0.43	0.050	
		-6.71	GMFCS 2	-13.70 : 0.29	0.060	
		1.60	GMFCS 3	-3.83 : 7.03	0.554	
		-4.14	GMFCS 4	-13.50 : 5.21	0.375	

B=regression parameter; CI = Confidence Interval; Δ = change from baseline; R^2 = R-square (the proportion of explained total variance explained by the final model)

** only those predictors that were correlated significantly ($p < 0.05$) or showed a trend for correlation ($p < 0.10$) with the mean change in GMFM66 (corrected for GMFM66 score at baseline) are included in the model*

Discussion

In an earlier randomised clinical trial we found that multilevel BTX-A injections and comprehensive rehabilitation in 46 children who walk with a flexed gait pattern had a positive overall effect on gross motor function⁷ (with significant improvements at 12 and 24 weeks) and on knee angle at midstance⁶ (with

significant improvements at 6 weeks). In the present study we found that only around 50% of these children were good responders at the corresponding follow-up points. To improve selection of the patients who are most likely to benefit from this intervention, we aimed to identify predictors for a good response. We evaluated all potential predictors (see Table 1) that have been suggested in the literature^{14, 15}. We only found age and ankle angle at midstance were found to be predictive of a favourable response on gross motor function and knee angle at midstance, respectively.

Age was associated in such a way that the treatment had a better medium term (12 weeks) effect on older children, increasing with 0.38 points on the GMFM66 per year of the child's age. This finding is of clinical relevance, because a child's natural course of gross motor function stabilizes at the age of approximately 8 years⁹, it supports the effectiveness of the treatment in the older age group. Fazzi et al.¹⁴, found that children of 4 years of age or younger improved significantly more on the GMFM66 than children over 4 years of age. In that study, young children (mean 5.4 years, \pm SD 3 years) were included. Although these results seem to contradict the findings in our study, we had excluded very young children (< 4 years). We found no association between age and change in knee extension at midstance. This supports the findings of Fazzi et al.¹⁵, who also only reported an age effect on gross motor function, and not on gait pattern.

Ankle angle at midstance was associated in such a way that the best longterm (48 weeks) effect was found in children with larger ankle dorsal flexion. However, the 0.21° increase in the knee angle at midstance, which results from a 1° increase in ankle (dorsi)flexion, is not clinically relevant, and should be interpreted with caution.

Furthermore, we found that initially (at 6 weeks) children with a higher baseline GMFM66 score improve less on the GMFM66 than children with a lower score. However, at 24 weeks they tend to improve more (without reaching significance; $p=0.07$), indicating that the effect was reversed. Perhaps, the higher level of motor

function eventually makes it easier to apply newly learned motor skills in the home situation. This long term effect seems to contradict with the findings of Fattal Falavski et al.¹⁴, who reported that children with lower scores on the GMFM improved most at 4 months after treatment. However, this was assessed according to the subjective experience of the parent.

As expected, the children with more knee flexion at baseline in the present study showed more improvement in knee angle at midstance than children with less knee flexion.

The predictive power of the different models was weak, explaining less than 20 - 40% of the total variance. This means that the improvements in gross motor function or knee angle at midstance are not strongly influenced by their baseline values and identified predictors (age and ankle angle at midstance, respectively). Moreover, the severity of motor involvement, the localisation of the motor disorder, the ROM, and the severity of spasticity, which have also been suggested as potential predictors in other studies¹³⁻¹⁵, were not predictive for any outcome at any of the different follow up points. This shows that it remains difficult to predict the effect of treatment with BTX A in children with CP. One limitation in this respect is that only 4 children in the present study had a unilateral spastic motor disorder, so the 'localisation of the motor disorder' was, in fact, not expected to correlate with the outcome.

in this study we also evaluated two other suggested potential predictors: gait kinematics and muscle strength¹³, neither of which were found to be predictive. However, it is questionable whether (functional) muscle strength was accurately measured with the squat test. It would probably have been better to measure to maximum number of squats (e.g. the repetition maximum).

Another limitation of this study is the relative small study group (n = 46). This might hamper adequate study power, although no more than 3 factors were included simultaneously in the multiple regression analysis, and none of the

remaining factors showed even a trend for association. So, even with a larger study group, the potentially of these factors to be an actual predictor is doubtful.

Despite the group descriptive analysis on responder-type, for which three categories were developed, we did not use logistic multilevel regression, as this would have lead to loss of information and in turn, loss of study power²⁰.

It is conceivable that other prognostic predictors might play an important role, such as degree of selective motor control¹² and level of balance or co-ordination. Therefore, more studies are needed to determine whether these patients' characteristics are prognostic for the desired effect in this specific patient group.

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Chapter 7

General discussion

General discussion

In the previous chapters of this thesis, the results of a randomised controlled trial (RCT), the BOLIEN study, were presented. In this trial, an intervention of multilevel botulinum toxin type A (BTX-A) injections and comprehensive rehabilitation was compared to usual care in children with spastic cerebral palsy (CP) who walk with a flexed knee gait. The main aim of the study was to assess the effectiveness of this intervention on mobility. The outcomes with regard to gait pattern, muscle length and spasticity were also measured, and determinants of the outcomes were studied. To assess spasticity, we developed the Spasticity Test (SPAT), a clinical instrument adapted from the original Tardieu Scale.

In this final chapter, the General Discussion, several methodological considerations and aspects of outcome assessment are discussed and the effectiveness of the multilevel BTX-A injections and comprehensive rehabilitation is evaluated. Furthermore, the clinical implications are also considered, and recommendations are made for future research.

Methodological considerations

We performed an RCT in which we evaluated the effects of multilevel BTX-A treatment and comprehensive rehabilitation or usual care in two comparable groups. However, our results may have been influenced by the heterogeneity of our study population, by the lack of blinded assessment, and by the complexity of the treatment.

Heterogeneity

Randomisation was successful with respect to the personal characteristics of our heterogeneous study group (see Table 1, Chapter 5). However, despite randomisation, the children in the control group had more knee flexion at baseline than the children in the intervention group (see Figure 2, Chapter 4). The amount of knee flexion at baseline was shown to be predictive of the amount of improvement in knee flexion after the BTX-A treatment (Chapter 6), in such a way that the children who had relatively greater knee flexion at the start of the intervention improved more in knee flexion after the treatment than the children with relatively less knee flexion. This implies that the control group is expected to improve even more after treatment. Therefore, our results with regard to the outcome on knee flexion might even be under-estimated, because the analyses were controlled for this baseline difference. The amount of knee flexion at baseline was not found to be predictive of the outcome on gross motor function (Chapter 6). We did not investigate whether or not knee flexion was a predictor of the effect on other outcomes (i.e. spasticity, muscle length, parent-percieved mobility, energy cost).

Blinding

The children in our study were assessed by multiple observers, who were employed in the centre of recruitment, and therefore their independency with respect to the participating children might be discussed. The observers were not blinded for treatment group, so the lack of blinding might have biased our results. However, this is only thought to be of marginal influence because the observers were experienced, fully trained and certified to assess the primary outcome, the score on the Gross Motor Function Measure-66¹ (GMFM-66). Moreover, the observers did not refer to any previous test values. However, the possible dependency of the observers, which was hampered by the limited staff available for the organization of the study, is thought to be of more substantial influence. Such

problems with regard to independency and blinding of the observers might be prevented in future research by obtaining financial support for additional research staff, such as independent research assistants.

Treatment

In the BOLIEN study, we formulated clear guidelines with regard to the BTX-A injections (e.g. individual target muscle selection; maximal dosage regimen; injection technique) and serial casting (e.g. method and maximum duration). Furthermore, we developed a physical therapy protocol, containing guidelines for the training program (e.g. intensity and treatment focus). In all these guidelines the heterogeneity of the patients was taken into account, offering individually tailored treatments according to the child's specific needs. Because all children with CP have their own specific needs, the exact content of the treatment cannot be described. Strict standardization of an intervention, in which a homogeneous group of patients receive the same experimental treatment, will ideally make it possible to assess the *efficacy* of this intervention under optimal circumstances. However, this does not provide an answer to questions about the *effectiveness* of the intervention, which closely reflects routine clinical practice, and is relevant for rehabilitation purposes.

With regard to the choice of treatment in the BOLIEN study, we were specifically interested in the effectiveness of multilevel BTX-A and comprehensive rehabilitation as a combined treatment package, because this was considered to be the best clinical practice for the patients in the participating rehabilitation centers. This treatment package aims to improve the underlying muscle imbalance caused by spasticity, and also to improve muscle weakness and muscle length, which is thought to be the main prerequisite to achieve an improvement in mobility. This treatment rationale has been explained in more detail in the Introduction part (Chapter 1). The combined treatment package was compared to usual care, which consisted of low-frequency physical therapy. Therefore, from the results of this

study we cannot assess the effectiveness of each individual component of the treatment package within the total treatment effect. In order to assess the effect of multilevel BTX-A injections in addition to comprehensive rehabilitation, a randomised controlled trial (RCT) should be performed, in which the control group should only receive the comprehensive rehabilitation (intensive physical therapy, orthoses and serial casting).

Outcome assessment

Assessing spasticity

A specific outcome of interest in this thesis was the clinical assessment of spasticity (Chapters 2 and 3). We explained in Chapter 2 that many different instruments that have been developed are used to assess spasticity in children with CP. A lack of consensus on the most appropriate instrument is illustrative of the ongoing discussion on how to measure ‘spasticity’. This discussion seems to be directly related to the, mainly semantic, discussion on the about the definition of spasticity.

In our study, spasticity was defined, according to Lance², as ‘a motor disorder characterised by a velocity dependent increase in tonic stretch reflexes (‘muscle tone’) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome (UMNS)’. The clinical symptom of spasticity in this definition is a velocity-dependent increase in muscle tone. However, the term ‘spasticity’ is also often used to indicate all or several symptoms of the UMNS (see Table 1, Chapter 2). To illustrate the ongoing debate, a European interdisciplinary research group has recently proposed a new, more general, definition, in which spasticity is defined as ‘intermittent or sustained involuntary activation of muscles’. Thus, in a addition to a velocity-

dependent increase in muscle tone, this definition also includes all other symptoms of abnormal muscle activity, such as non-velocity-dependent increased muscle tone (e.g. hypertonia) and clonus. By doing so, the term 'spasticity' becomes a synonym for the excess symptoms (signs of abnormal involuntary muscle activation) of the UMNS³. We believe that this leads to considerable confusion⁴. Moreover, it is clear that these symptoms can exist independent of each other, and do not necessarily share a common pathophysiology (Chapter 2).

We therefore wish to emphasise that the formulation a clear and unambiguous definition of spasticity is the first step in reaching consensus on the appropriate method of clinical spasticity assessment, and that the definition should describe what one attempts to assess. Although it is not our intention to propose a new definition of spasticity, we feel that further clinical confusion may well be avoided if the *clinical* evaluation and definition of spasticity is restricted to a '*velocity-dependent increased resistance to passive stretch*' when passively manipulating a muscle. This velocity-dependency has been validated in many studies⁵⁻⁸, by showing that stretching a muscle at a sufficiently high velocity is essential in order to elicit a stretch reflex at a certain angle in the range of motion (ROM), and the faster the stretch, the earlier and stronger the reflex component of the increased muscle tone will be. It is especially important to assess spasticity with a fast passive stretch, in order to detect the dominant phenomenon of spasticity: the 'catch'. The catch is defined as a sudden appearance of increased resistance in response to a fast passive stretch at a certain angle ('angle of the catch' [AOC]) before the end ROM, which stops the movement immediately^{5,9}. Any clinical assessment of spasticity should verify this velocity-dependency, by comparing and grading the intensity of the muscle tone elicited at a very slow and a very fast passive muscle stretch, and measuring the AOC in relation to the ROM of that muscle. Both angular velocities should be well defined and standardised.

The outcome of the review described in Chapter 2 of this thesis showed that the most frequently used Ashworth and Modified Ashworth Scales are inadequate for

the measurement of spasticity, because they assess resistance to passive stretch, at only at one (undefined) velocity, thereby not demonstrating the velocity-dependent character. Moreover, these methods often lack an adequate description of the testing procedure, which hampers correct interpretation of the results and limits their use for clinicians and researchers.

Based on these grounds, we developed a clinical spasticity assessment scale, based on the original Tardieu Scale¹⁰: the Spasticity Test (SPAT). This scale has a well defined assessment protocol, and assesses the muscle during two passive stretches. We tested the feasibility and reliability of the SPAT, and concluded that an experienced examiner can use the SPAT to make a reliable assessment of the hamstrings and calf muscles, but for adductor-testing a simplified version of the SPAT is recommended. Unfortunately, the SPAT is not reliable for the measurement of the rectus femoris, but as present, no clinical alternative can be suggested. When an assessment is made by two examiners with different levels of experience, the SPAT is only reliable for the gastrocnemius muscle. A possible explanation for this low (inter-rater) reliability is the test's presumed susceptibility to practise effects¹¹, but this should be studied in future research. Another explanation is that the applied velocities varied between the observers, despite the standardisation in the written guidelines. Measurement of the angular velocities and assessment of reliability in a clinical setting is therefore the main challenge for future studies.

Assessing mobility

The main outcome of interest in this study was the assessment of *mobility*. For this purpose, the GMFM-66¹ was used. At the moment, this is one of the most appropriate measures for this purpose in patients with CP, because it has been validated in this patient group for the measurement of changes of gross motor function over time. The GMFM66 is a *capacity* measure: it assess abilities in a controlled evaluative setting, but it gives no information about the actual

performance in daily life¹². A child's 'capacity' indicates the highest probable level of what the child can do in a controlled environment, whereas a child's 'performance' describes what the child does in the everyday setting. Relating this to the results of the BOLIEN study, we know that multilevel BTX-A and comprehensive rehabilitation improved the children's capacity in standing, walking, jumping or running, but does this also mean that they walk more indoors or outdoors, or that they climb stairs or run more frequently? This question cannot be answered from the results of this study because we did not measure *performance*. The known ceiling-effect of the Pediatric Evaluation Disability Inventory¹³ (PEDI) in children over 7.5 years of age and/or with a higher level of motor function, limited its usefulness as an outcome measure for that purpose in our study. Nevertheless, changes on our secondary outcome measure, the Problem Score (Chapter 5), which was rated on an internationally accepted Visual Analogue Scoring (VAS) scale, suggests that these children also improved in mobility *performance*. Although the Problem Score is subjective, and its reliability has not yet been studied, the reported problems are parent-perceived and based on the performance of daily tasks, which varied from walking certain distances and climbing stairs, to playing outdoors.

Effectiveness of multilevel BTX-A and comprehensive rehabilitation

In the BOLIEN study, the effect of the intervention on mobility was statistically significant, as measured with the GMFM-66. The improvements at the different follow-up points were rather small (e.g. range 2.1 - 3.5 points), but nevertheless they are clinically relevant¹⁴. These effects were observed over a period between 12 and 48 weeks after BTX-A treatment. Over this entire period, 50% of the study

participants had improved. We feel that a 50% improvement is rewarding, and this is also supported by the considerable improvements (proportional changes up to 25%) on the secondary problem score. Although theoretically both outcomes may differ in the information they provide with regard to mobility (i.e. capacity and performance, as was explained earlier), the latter outcome suggests that the intervention also improved mobility of the children in daily life, as perceived by the parents, and this is therefore an important finding. It is noteworthy that no treatment effect (positive nor negative) was found on the energy cost of walking during the first 24 weeks of follow-up. These findings are in accordance with the results reported in the literature¹⁵. This might indicate that an improved gait pattern or improved mobility does not necessarily lead to an improvement in energy cost, although this is generally assumed. However, further analyses did show a positive treatment effect on energy cost for the whole group at the 48-week follow-up (no control group). Moreover, it was shown that only the more severely affected children (GMFCS level III) seemed to improve at this point (Chapter 5). Therefore, it is possible that the lack of effect during the first 24 weeks is influenced by the low number of children, in particular the more severely affected children.

Nevertheless, according to the GMFM-66, 50% of the study participants were still classified as 'non responders'. Surprisingly, additional analysis showed that of all the patient characteristics that were thought to be predictive of this outcome, only age appeared to be so. We found that the children who were relatively older at the start of the intervention benefited more from the treatment than the children who were relatively younger (Chapter 6). This effect was only present at the 12-week follow-up. This age-effect is not in agreement with the effect reported in another study¹⁶, but in that study a different outcome measure was used. It is conceivable that other prognostic predictors, which were not (accurately) evaluated in our study, might play an important role, such as degree of selective motor control¹⁷, muscle strength¹⁸, and also level of balance or co-ordination. It is

important to gain insight into these characteristics of responders and non-responders. Therefore, new studies are needed to determine whether these patient characteristics are prognostic for the desired effect in this specific patient group.

In addition to the improvement in mobility, treatment with multilevel BTX-A and comprehensive rehabilitation in the BOLIEN study also resulted in changes in gait pattern, muscle length and spasticity. The significant improvement in these impairment outcomes was demonstrated immediately at the first 6-week follow-up (Chapter 4), unlike the improvements in mobility, which were demonstrated somewhat later at 12-week follow-up (Chapter 5). The (clinically more relevant) changes in mobility continued up to 24 weeks, whereas the improvement in the level of impairment had mainly relapsed at that point. This long-term effectiveness on mobility is clinically important. It shows that, even though the pharmacological effect of BTX-A had worn off and the intensified physical therapy was discontinued, there was still a potential for further improvement in mobility. It seems plausible that the initial improvements in spasticity and muscle length restored the underlying muscle balance, at least to some extent. Increased muscle strength is also thought to add to this restored muscle balance, but muscle strength was not assessed as an outcome measure in this study. The restored muscle balance possibly led to an improvement in gait pattern and offered a starting point for improvement in (existing) motor skills during therapy, which through practise become more routine in daily life, leading to an improvement in mobility. However, the inter-relationships between these different impairment and mobility outcomes, and their apparent difference in timing of the recorded effect (e.g. the point in time when a significant change was measured) have not been addressed been addressed in our study. The relationship between impairment and activity is known to be complex, and the heterogeneity in clinical presentation of the various impairments in children with CP further complicates this evaluation. Nonetheless, gaining more knowledge about the relationship between impairments and activity in these children may help us to provide a more profound scientific

base for the fine-tuning of our treatment, in order to achieve more effective results. For example: if muscle weakness is found to influence the flexed knee gait pattern to a greater extent than spasticity, physicians might want to focus more on muscle-strengthening exercises than on the reduction of spasticity.

Final conclusions, implications and recommendations

This thesis showed that a combined treatment package of multilevel BTX-A and comprehensive rehabilitation is effective in children with CP who walk with a flexed knee gait. There was an immediate positive effect on spasticity, muscle length and gait pattern, and a longer-lasting improvement in mobility (for at least six months, and probably even for one year). In children aged 4 to 12, the older children are more likely to benefit in terms of improvement in mobility, but all children will benefit equally in terms improvement in gait pattern.

This thesis also provided useful insight into issues regarding the clinical assessment of spasticity. In order to assess spasticity clinically, and to assess the velocity-dependent increased resistance to passive stretch, the muscle response should be measured at two different velocities of muscle stretch.

Clinical Implications

The (relevant) positive effect on the GMFM-66 in children who walk with a flexed knee gait shows that improvement in mobility is possible after multilevel BTX-A and comprehensive rehabilitation treatment. At present, however, the

fundamental, active components of this combined treatment package are not clear. Implementation of the total combined treatment approach is therefore recommended in the daily rehabilitation of children with CP who walking with flexion of the knees during midstance, when their need is to improve, or maintain, their level of mobility. For structural implementation, we recommend the use of the clinical guidelines described in Chapters 4 and 5 on patient selection, BTX-A dosage, target muscle selection, the prescription of orthosis, serial casting, and the physical therapy program. The guidelines for the maximum dosage of BTX-A are consistent with the recently developed European consensus on best practice for BTX-A treatment of CP¹⁹, and with the Dutch concept guidelines for the treatment of children with spastic CP²⁰. It should be noted that successful implementation consequently requires a multidisciplinary team approach, consisting of a rehabilitation physician, a physical therapist, and an orthotist. Furthermore, prerequisites for selections should be good motivation of the children and their parents/caregivers and their intention to comply with the treatment program, in particular with the intensive physical therapy program. Moreover, because the improvement in mobility is not an immediate effect, their motivation may need to be continuously stimulation throughout the treatment period.

Furthermore, we recommend the use of the SPAT as a clinical measurement of spasticity in both clinical practice and research. However, we do suggest that the observers should receive adequate training before starting the actual assessments, and that the detailed standardised procedure is adhered to. This is especially important for research purposes. However, because of its low interrater reliability, we recommend that, when the SPAT is used for research purposes, all the assessments of a patient are performed by the same observer.

Recommendations for future research

- Further RCTs should be performed to study the contribution of each of the individual components of the combined treatment package to the total treatment effect. In particular, the effect of the combined multilevel BTX-A and comprehensive rehabilitation, compared to the effect of comprehensive rehabilitation alone, should be investigated. In these studies, muscle strength and degree of selective motor control should also be included as an outcome measure.
- Further research should be carried out to study the relationships between the changes in gait pattern, spasticity, muscle strength and muscle length (level of impairment) on one hand, and the changes in mobility (level of activity level) on the other hand.
- More research is needed to identify possible predictors (e.g. muscle strength, selective motor control, co-ordination) of a favourable effect of multilevel BTX-A and comprehensive rehabilitation, especially on mobility.
- More attention should be paid to optimisation of the different components of the comprehensive rehabilitation. With regard to physical therapy, future studies should address the aspects of optimal duration, frequency, intensity and form (e.g. strength training, endurance training, co-ordination training, flexibility training, gait training).
- Future research should further investigate the validity and reliability of the SPAT. At present, plans have been made for continuing research to standardise the two velocities of stretch, and to develop a training program for assessors to improve the SPAT's reliability. Furthermore, the construct validity, the responsiveness (sensitivity to change), and the minimal clinically important change should be investigated.

- Future research should also focus on the development and validation of instruments to assess mobility performance in children with CP. They should have good feasibility for use in clinical and research settings, and be applicable for children of all ages. For this purpose, subjective instruments based on child or parent self-assessment, such as the problem score, should be refined and further tested. More objective measures, such as activity monitoring, could also be of value, in particular in the research setting. An activity monitor is a portable device that provides an objective evaluation of the amount of daily activity, such as running, walking, standing, sitting, lying down, etc. This measure has been already validated for use in non-cerebral palsied paediatric populations^{21,22}, so future research should aim to validate this instrument for use in the cerebral palsied population.

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Summary

Most children with spastic cerebral palsy (CP) have a deviating gait pattern, and one of the typical patterns is a flexed knee gait. Children who walk with a flexed knee gait are specifically at risk of deteriorating in mobility. To prevent this (potential) deterioration, treatment is indicated at an early stage. It is postulated that the cause of this gait pattern is attributable to a combination of abnormal involuntary muscle activity (such as spasticity), muscle weakness and/or reduced muscle length. In this, spasticity is defined as 'a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome'. This is clinically recognisable as a velocity-dependent increase in muscle tone in response to muscle stretch, demonstrated at a certain angle in the range of motion (ROM).

The presence and severity of spasticity and other impaired muscle functions vary per patient. Nonetheless, characteristic for all patients with CP is that the impairments are not equally spread throughout their muscles. This results in a muscle imbalance, for instance in an agonist-antagonist couple (such as flexor-extensor) there is generally more spasticity and/or shortening in one muscle than in the other. Treatment of this muscle imbalance is considered to be the main prerequisite for a potential improvement in mobility. The treatment rationale is therefore to aim at decreasing the muscle activity in spastic (usually flexor) muscles, stretching the shortened (usually flexor) muscles, and strengthening the weakened (usually extensor) muscles at the same time. To decrease spasticity, botulinum toxin type A (BTX-A) can be injected in the muscle, and a comprehensive rehabilitation treatment, consisting of intensive physical therapy, orthosis and serial casting, can be used to train the weaker extensor muscles, stretch the shorter flexor muscles and increase mobility.

In this thesis it was hypothesized that treatment with multilevel BTX-A and comprehensive rehabilitation will improve spasticity, muscle length and the flexed knee gait pattern, which in turn is hypothesized to improve activities in the domain

of mobility. Multilevel BTX-A treatment refers to the injection of multiple muscles (around the hip, knee and ankle) within one treatment session, and is particularly indicated for children with a gait which is characterized by flexion of the knee in midstance. For the evaluation of spasticity, an appropriate measurement instrument was needed. Since the characteristics of patients with CP differ widely, it is likely that certain patients will benefit more than others from multilevel BTX-A and comprehensive rehabilitation.

This thesis therefore evaluates:

1. the available instruments for the clinical assessment of spasticity in children with CP, and their compliance with the velocity-dependent concept of spasticity (Chapter 2)
2. the reliability of a new instrument for the clinical assessment of spasticity in children with CP (Chapter 3)
3. the effects of multilevel BTX-A and comprehensive rehabilitation on spasticity, muscle length and gait pattern in children with CP who walk with a flexed knee gait (Chapter 4)
4. the effect of multilevel BTX-A and comprehensive rehabilitation on mobility in children with CP who walk with a flexed knee gait (Chapter 5)
5. the predictors of multilevel BTX-A and comprehensive rehabilitation on gait pattern and mobility in children with CP who walk with a flexed knee gait (Chapter 6)

The most widely accepted definition of spasticity was formulated by Lance in 1980. In this definition, he defined spasticity as the clinical symptom of a velocity-dependent increase in muscle tone at passive stretch. Elaborating on this definition to include a clinical assessment of spasticity implies grading the intensity of the muscle tone and comparing it at different passive velocity stretches. Although ignored in Lance's definition, the patient's testing posture and

the initial length from which the muscle is stretched are both of significant influence on spasticity.

Chapter 2 presents the results of a critical review of the various clinical instruments that are used to evaluate spasticity in children with CP. The purpose of this study was to evaluate whether these clinical instruments assess spasticity in accordance with the velocity-dependency as defined by Lance, and whether these assessments are properly standardized. The various clinical instruments were identified through systematic literature searches, and evaluated on: 1) whether the assessment was made at different standardized velocities of passive stretch, 2) whether a standardized testing posture was defined, and 3) how spasticity was quantified.

Thirteen clinical spasticity assessment instruments were identified and evaluated. Most of these instruments, including the mostly frequently used Ashworth Scale (AS) and the Modified Ashworth Scale (MAS), do not comply with the concept of spasticity, as defined by Lance. They grade muscle tone only at one (often non-specified) velocity of passive stretch. Only the Tardieu Scale (TS) measures the velocity-dependent increase in muscle tone and compares the intensity and the angle of appearance of the increased muscle tone at (three) different velocities. However, these velocities have not been fully standardized. With respect to the standardised posture, the TS assesses patients in two positions: sitting and lying. With respect to quantification, the TS produces separate scores for both tone intensity and ROM at different velocities. However, these are used ambiguously by different users.

In conclusion, only the original TS is a suitable instrument for the assessment of spasticity, since it grades muscle tone intensity and ROM at three different velocities. However, the original testing protocol has a comprehensive and time-consuming clinical scoring system.

Although the velocity-dependent characteristic of spasticity can only be studied by stretching the muscle at two different velocities, e.g. slow and fast, it is especially important to test spasticity with a fast passive stretch. This makes it possible to detect the dominant phenomenon of spasticity: the 'catch', a sudden appearance of increased resistance in response to a fast passive stretch at a certain angle before the end ROM, which stops the movement immediately. Based on this rationale, a new spasticity assessment instrument was developed, the Spasticity Test (SPAT), which was based on the TS.

Chapter 3 describes the feasibility and reliability of the SPAT in five leg muscles. With this instrument, the muscle is first passively stretched at a slow velocity (≥ 3 seconds) to measure the maximum ROM. Spasticity is then assessed during a passive stretch at a fast velocity (< 1 second) to measure the joint angle of the catch (AOC) and to grade the intensity of the muscle resistance on a 4-point (0,1,2,3) spasticity scale. The SPAT has a standardized testing protocol describing the patient and observer position for each muscle tested, as well as describing the ROM and AOC measurement, using hand-held goniometry.

Twenty children with a diagnosis of spastic paresis were included in this study. They were all tested three times on one day by two different observers. In each session, the ROMs of five leg muscles were assessed (hamstrings, short adductors, soleus, gastrocnemius and rectus femoris muscles), after which spasticity was assessed with the spasticity scale and the AOCs. In all the tests the goniometry was performed by a third observer. Reliability was expressed in absolute agreement (AA) (only for the spasticity scale), and in Intraclass Correlation Coefficients (ICCs) and Standard Errors of Measurement (SEMs).

The SPAT was easy to administer, and the assessment was performed in 5 to 8 minutes. The intra-rater reliability was good for the hamstrings, soleus and gastrocnemius muscles (ROM: SEM range 2.9° - 5.1° , spasticity scale: AA 70% - 95%, AOC: SEM 4.8° - 6.4°). When the spasticity scale was simplified to a 2-point (0,1) scale rating the absence or presence of a catch, the intra-rater reliability was

also good for the adductor muscle, but not for the rectus femoris muscle. The inter-rater reliability was only good for the gastrocnemius muscle (ROM: SEM 4.0°, spasticity scale: AA 65%, AOC: SEM 3.6°). These results show that repeated SPAT measurements should be performed by the same trained examiner. In conclusion, when applied by one examiner, the new SPAT is a feasible and reliable clinical instrument to measure spasticity for all of the leg muscles studied, except for the rectus femoris muscle. To improve inter-rater reliability, we suggest that a special training programme for examiners should be developed, and that the velocity of the stretch should be further standardized by means of a measurement device.

Chapters 4 and 5 present the results of a multi-centre randomized controlled trial on the effect of multilevel BTX-A injections and comprehensive rehabilitation in children with CP who walk with a flexion pattern. Forty-six children were included in this study. The inclusion criteria were: diagnosis of CP; ability to walk (with or without a walking aid or an ankle-foot orthoses); gait characterized by persistent flexion of the knee in midstance; age between 4 and 12 years; spasticity in two or more leg muscles interfering with mobility; with an indication for multilevel BTX-A. The children were randomly assigned to the intervention or the control group. The intervention group was treated with multilevel BTX-A injections and comprehensive rehabilitation. The comprehensive rehabilitation consisted of a 12-week period of intensive physical therapy according to a standardized protocol, orthoses and, if necessary (i.e. if the ROM of the gastrocnemius muscle was less than 0° dorsiflexion), serial casting. Children in the intervention group were assessed twice during a 6-week baseline period, and there were 4 follow-up measurements at 6, 12, 24 and 48 weeks after the injections. The control group continued to receive usual care (low intensity physical therapy, some used orthoses) for a period of 18 to 30 weeks. They were assessed every 6 weeks. After this baseline period, the children in the control group were also treated with

multilevel BTX-A and comprehensive rehabilitation, with a follow up at 6, 12, 24 and 48 weeks after treatment.

Chapter 4 first evaluates the effect of multilevel BTX-A and comprehensive rehabilitation on gait pattern, muscle length and spasticity, as opposed to usual care. For the purpose of this study, the effect in the intervention group ($n=23$) up to 24 weeks after treatment was compared with the effect of usual care in the control group ($n=23$).

The gait pattern was evaluated with the Edinburgh Visual Gait Analysis Interval Testing (GAIT) scale. Knee angle at midstance, ankle angle at midstance, knee angle at terminal stance, and hip rotation at terminal swing were also measured. Muscle length and spasticity were assessed with two components of the SPAT; the ROM during a slow passive stretch (> 3 sec) and the AOC during a fast (<1 sec) passive stretch, respectively.

After 6 weeks there was a significant improvement in the quality of the gait pattern (1.7 points improvement on the GAIT score, $p < 0.01$) and in the gait kinematics during midstance (7° improved knee extension, $p < 0.01$) and terminal swing (5° improved knee extension, $p < 0.01$, and 4° improved hip rotation, $p = 0.02$). The 7° improvement in knee extension at midstance, in particular, was found to be clinically relevant. No effect was found at 24 weeks, but it is likely that this second assessment was too late to demonstrate sustained improvement, because no gait assessment was performed at 12 weeks. A significant effect in muscle length was found at 6 weeks: muscle length improved in the hamstrings (9° , $p < 0.01$) and in the gastrocnemius muscles (5° , $p < 0.01$), and both improvements were maintained up to 24 week after treatment. These changes were found to be clinically relevant. No change was found in the length of the rectus femoris and adductor muscles, but since these muscle lengths were both normal at baseline this was to be expected. A reduction in spasticity was found at 6 and 12 weeks in the injected hamstrings (11° , $p < 0.01$) and gastrocnemius muscles (6° , $p = 0.01$). This

could be expected because of the pharmacological mechanism of BTX-A, which is known to be only temporary. An additional effect was found in the uninjected soleus muscles (5° , $p = 0.02$), which could be due to diffusion of BTX-A from the injected gastrocnemius muscle.

Based on the results of this study, multilevel BTX-A and comprehensive rehabilitation (as opposed to usual care) is effective in improving gait pattern, increasing the muscle length of shortened muscles and decreasing spasticity in injected muscles in children who walk with flexed knees. Of these effects, only the effect on muscle length was still present after 24 weeks.

Subsequently, Chapter 5 evaluates the effectiveness of multilevel BTX-A injections and comprehensive rehabilitation on mobility. For the purpose of this study, the effect in the intervention group ($n=23$) up to 24 weeks after treatment was compared with the effect of usual care in the control group ($n=23$) (e.g. trial analysis). The uncontrolled long-term effect at 48 weeks after treatment was also evaluated within the total group ($n=46$) (e.g. before-after analysis). Finally, subgroup analysis for the level of Gross Motor Function Classification System (GMFCS) and age were performed to detect differences in treatment effect between the groups.

The primary outcome for mobility was the Gross Motor Function Measure-66 (GMFM66). The secondary outcomes were the energy cost of walking (measured in a sub-group of 21 children) and a parent self-reported problem score (0-10 scale).

The trial analysis showed a significant treatment effect on mobility (GMFM66) in favour of the intervention group at 12 and 24 weeks (2.1, $p=0.02$ and 3.5 points, $p < 0.01$ respectively). This was also found on the problem score (-1.8 and -1.7 points, $p < 0.01$ respectively). The effect on both outcomes were considered to be clinically relevant. No treatment effect was found on energy cost. The before-after analysis also showed long-term (i.e. 48 weeks after treatment) effects on these outcomes (GMFM-66 2.3 points, $p < 0.01$; PS -1.4 points, $p < 0.01$), and there was also a long-

term significant effect on energy cost (-1.8 J/kg/m , $p < 0.01$). However, these long-term findings should be confirmed in a randomized controlled study. With respect to the effect on energy cost 48 weeks after treatment, it was found that children who used walking aids (GMFCS level III) improved significantly more than children walking without aids (GMFCS levels I and II). A possible explanation for this is that children in the latter group seem to be non-responsive to change in energy cost because their energy cost is already low, although it is higher than that of healthy children.

Based on the results of this study, multilevel BTX-A and comprehensive rehabilitation (as opposed to usual care) is an effective method of treatment that leads to clinically relevant improvements in mobility, in terms of GMFM-66 score and parent-perceived mobility problems, in children who walk with flexed knees. Conversely, it does not effect the energy cost of walking.

Patients with spastic CP are very heterogeneous with respect to the severity of impaired muscle functions, localisation of the motor disorder, and the severity of motor involvement. Therefore, it is likely that certain patients will benefit more than others from multilevel BTX-A and comprehensive rehabilitation. **Chapter 6** describes a study in which an attempt was made to identify predictors for a favourable outcome of multilevel BTX-A injections and comprehensive rehabilitation on gross motor function (measured with the Gross Motor Function Measure (GMFM66)) and gait pattern (assessed according to the knee angle at midstance) in children who walk with a flexed knee gait. For this purpose, we used follow-up data (6, 12, 24 and 48 weeks after treatment) from the total group ($n=46$) in the randomized controlled trial as described in chapters 4 and 5. All in the literature suggested factors were considered to be possible predictors of outcome: age, gender, severity of motor involvement, localisation of the motor disorder, level of motor function, muscle strength, ROM, spasticity, and gait kinematics.

Of all the potential predictors, only age and ankle angle at midstance were found to be predictive of an improvement in gross motor function and gait pattern, respectively. Age was associated in such a way that the treatment had a better medium-term (12 weeks) effect on older children, increasing with 0.4 points on the GMFM66 per year of the child's age (on condition that other factors remain unchanged). This finding was considered to be clinically relevant. Ankle angle at midstance was associated with gait pattern in such a way that the best long-term (48 weeks) effect was found in children with increased ankle dorsal flexion. However, the 0.21° increase towards knee extension, which results from a 1° increase in ankle dorsiflexion, was not clinically relevant. The predictive power of the different models was weak, explaining less than 20-40% of the total variance. Moreover, none of the potential predictors gender, severity of motor involvement, localisation of the motor disorder, ROM, and spasticity were found predictive for any outcome at any of the different follow-up points.

Based on these results, the only relevant significant predictor for a favourable response of multilevel BTX-A injections and comprehensive rehabilitation in this patient group, with regard to gross motor function, is older age.

In **Chapter 7** provides the general discussion. Several methodological considerations and aspects of outcome assessment were discussed and the effectiveness of the multilevel BTX-A injections and comprehensive rehabilitation was evaluated. It was concluded that a combined treatment package of multilevel BTX-A and comprehensive rehabilitation is effective in obtaining improvements in mobility in children with CP who walk with a flexed knee gait. With regard to the clinical assessment of spasticity, it was concluded that the velocity-dependent increased resistance to passive stretch should always be assessed by measuring the muscle response at two different velocities of muscle stretch. Furthermore, chapter 7 discussed the clinical implications, and formulated recommendations for future research.

Samenvatting

Veel kinderen met een spastische cerebrale parese (CP) hebben een afwijkend looppatroon. Eén van de meest typerende looppatronen is het zogenaamde ‘flexie-patroon’. Het is bekend dat kinderen die lopen met een flexie-patroon tijdens hun ontwikkeling een verhoogd risico hebben op een achteruitgang in hun mobiliteit. Vroegtijdige behandeling is daarom essentieel om deze (dreigende) achteruitgang te voorkomen. De oorzaak van het flexie-patroon is vermoedelijk een combinatie van abnormale onwillekeurige spier-activiteit zoals spasticiteit, in combinatie met spierzwakte en/of afgenomen spierlengte. Het begrip spasticiteit wordt hier gedefinieerd als ‘een motorische stoornis, gekenmerkt door een snelheidsafhankelijke toename in tonische rek reflexen (spiertonus) met verhoogde peesreflexen, als gevolg van overprikkelbaarheid van de rekreflex, als een onderdeel van een centraal motorische parese’. Spasticiteit in een spier is klinisch te herkennen als een snelheidsafhankelijke toename in spiertonus wanneer deze spier passief gerekt wordt. Deze verhoogde spiertonus treedt op bij een bepaalde hoek in de range of motion (ROM) van die spier.

De aanwezigheid en ernst van spasticiteit, als ook die van andere spierfunctiestoornissen, varieert per patiënt. Hierdoor heeft elke patiënt een uniek klinisch beeld. Wel is het zo dat alle patiënten met CP kenmerkt worden door het feit dat de spierfunctiestoornissen nooit gelijk verdeeld zijn over de verschillende spieren, wat leidt tot een dysbalans in de spieren. Bijvoorbeeld, in een agonist-antagonist koppel (zoals een flexor-extensor koppel) is de spasticiteit en/of spierversporing in de ene spier vaak groter dan in de andere spier. Behandeling van deze spier-dysbalans wordt als het belangrijkste uitgangspunt genomen voor een mogelijke verbetering in mobiliteit van de patiënt. De opzet van de behandeling is daarom gericht op het verbeteren van de spierbalans, door *gelijktijdig* de overmatige spieractiviteit van de spastische spieren (meestal de flexoren) te verminderen, de verkorte spieren (meestal de extensoren) op te rekken, en de zwakke spieren te versterken (meestal de extensoren). Eén van de mogelijkheden om spasticiteit te verminderen, is door botuline toxine type A (BTX-

A) te injecteren in die spier. Wanneer meerdere spieren, werkend over meerdere gewrichten (rondom heup, knie en enkel), tijdens één behandelsessie geïnjecteerd worden, spreekt men van multilevel BTX-A. Na injectie volgt een revalidatieprogramma, gericht op het verbeteren van de mobiliteit. Dit bestaat uit het (1) aanmeten van orthoses ('spalken'), (2) een periode van redressiegips-behandeling, en (3) een periode van intensieve fysiotherapie waarin door middel van rekken de verkorte flexoren worden verlengd, en door middel van training de zwakke extensoren worden versterkt.

In dit proefschrift werd verwacht dat behandeling met multilevel BTX-A injecties en revalidatie een positief effect heeft op spasticiteit (afname), spierlengte (toename) en looppatroon (verbetering), waardoor een verbetering van mobiliteit wordt verwacht. Deze behandeling is vooral geïndiceerd bij kinderen lopend met een flexie-patroon, en daarom zijn zij de focus van dit proefschrift. In dit proefschrift wordt het volgende geëvalueerd:

- (1) Wat zijn de klinische instrumenten voor het meten van spasticiteit bij kinderen met CP, en wordt hiermee het snelheidsafhankelijke karakter van spasticiteit vastgelegd? (Hoofdstuk 2)
- (2) Wat is de betrouwbaarheid van een nieuw meetinstrument om klinisch spasticiteit te meten bij kinderen met CP? (Hoofdstuk 3)
- (3) Wat is het effect van multilevel BTX-A injecties en revalidatie op spasticiteit, spierlengte en looppatroon bij kinderen met CP lopend met een flexie-patroon? (Hoofdstuk 4)
- (4) Wat is het effect van multilevel BTX-A injecties en revalidatie op mobiliteit bij kinderen met CP lopend met een flexie-patroon? (Hoofdstuk 5)
- (5) Zijn er factoren die het effect voorspellen van multilevel BTX-A injecties en revalidatie op looppatroon en mobiliteit bij kinderen met CP lopend met een flexie-patroon? (Hoofdstuk 6)

De meest gebruikte definitie van spasticiteit werd geformuleerd door Lance in 1980, waarin spasticiteit gedefinieerd werd als een klinisch symptoom, gekenmerkt door een snelheidsafhankelijke toename van spiertonus bij passieve rek van die spier. Wanneer we volgens deze definitie spasticiteit willen meten, moeten we de intensiteit van de spiertonus zowel scoren als vergelijken bij verschillende snelheden van passieve rek. Belangrijk hierbij is dat zowel de *lengte* van waaruit de spier gerekt wordt als de *uitgangshouding* van de patiënt van substantiële invloed zijn op de ernst van de spasticiteit, ook al wordt dit niet zo duidelijk benoemd in de definitie van Lance.

Hoofdstuk 2 beschrijft de resultaten van een kritische review over de verschillende klinische meetinstrumenten die gebruikt worden om spasticiteit te meten bij kinderen met CP. Het doel van deze studie was om te evalueren of deze meetinstrumenten het snelheidsafhankelijke concept van spasticiteit meten, zoals gedefinieerd door Lance, en of deze meetinstrumenten voldoende zijn gestandaardiseerd. De verschillende meetinstrumenten zijn eerst verzameld met een systematische zoekstrategie in de literatuur, en vervolgens geëvalueerd op: (1) of de afname geschiedde onder verschillende snelheden van passieve rek, (2) of de uitgangshouding van de patiënt was gedefinieerd, en (3) op welke manier spasticiteit werd gekwantificeerd.

Dertien verschillende klinische meetinstrumenten voor spasticiteit werden geïdentificeerd en geëvalueerd. Het merendeel van deze instrumenten, waaronder de meest gebruikte Ashworth Schaal (AS) en de gemodificeerde Ashworth Schaal (MAS), voldoen niet aan het concept spasticiteit, zoals gedefinieerd door Lance. Deze schalen evalueren spasticiteit slechts bij één (veelal ongespecificeerde) snelheid van passieve rek. Alleen de Tardieu Schaal (TS) evalueert spasticiteit door de intensiteit van de spiertonus én de hoek waarbij deze optreedt in de ROM te vergelijken bij drie verschillende snelheden van passieve rek. Desondanks zijn de verschillende snelheden in de TS niet duidelijk gestandaardiseerd. Bovendien wordt deze test uitgevoerd bij twee verschillende uitgangshoudingen van de

patiënt: in een zittende en in een liggende positie. Met betrekking tot de kwantificatie beschrijft de TS het gebruik van verschillende scores voor intensiteit en ROM bij de drie verschillende snelheden: deze worden echter door de gebruikers inconsequent gebruikt.

De conclusie van deze studie is dat de TS weliswaar een geschikt instrument is om klinisch spasticiteit te meten, aangezien het de spiertonus en ROM evalueert bij drie verschillende snelheden, maar helaas een heel uitgebreid en tijdsintensief klinisch scoringssysteem heeft.

Ondanks dat de snelheidsafhankelijke eigenschap van spasticiteit alleen bestudeerd kan worden door de spier met verschillende snelheden te rekken, dat wil zeggen *langzaam* en *snel*, is met name de snelle rek van belang bij het meten van spasticiteit. Hierdoor kan men namelijk het meest prominente fenomeen van spasticiteit opsporen: de 'catch'. Dit is een plotselinge toename van verhoogde weerstand in reactie op een snelle rek van een spier, welke optreedt op een bepaalde hoek vóór het eind van de ROM, en welke verdere beweging direct stopt. Dit fenomeen is genomen als basis bij het ontwikkelen van een nieuw meetinstrument, de Spasticiteit Test (SPAT), welke is gebaseerd op de Tardieu Schaal.

Hoofdstuk 3 beschrijft de toepasbaarheid en de betrouwbaarheid van de SPAT in vijf beenspieren. Met dit instrument wordt de spier eerst passief gerekt met een langzame snelheid (> 3 seconden) om de ROM te meten. Vervolgens wordt spasticiteit opgewekt door de spier heel snel te rekken (in < 1 seconde). Hierbij wordt eerst de hoek gemeten waarbij de catch optreedt (angle of the catch, AOC). Vervolgens wordt de intensiteit van deze spierreactie gescoord op een 4-punts spasticiteitschaal (0,1,2,3). De SPAT heeft een gestandaardiseerd meetprotocol: de uitgangsposities van patiënt en uitvoerder zijn per spier beschreven, daarnaast is ook de ROM en AOC bepaling met gebruik van hand-held-goniometrie beschreven.

Twintig kinderen met de diagnose spastische parese zijn geïncludeerd in deze studie. Allen zijn drie keer op dezelfde dag gemeten door twee verschillende uitvoerders. De goniometrie werd in alle drie sessies uitgevoerd door een derde uitvoerder. In elke sessie werden eerst de ROMs van vijf beenspieren (hamstrings, adductoren, soleus, gastrocnemius, rectus femoris) gemeten. Vervolgens werd de spasticiteit gemeten met de AOCs en de spasticiteitschaal. Betrouwbaarheid werd uitgedrukt in Absolute Agreement (AA) (alleen voor de spasticiteitschaal), en de Intraclass Correlatie Coëfficiënten (ICCs) en de Standard Error of Measurement (SEMs).

De SPAT was gemakkelijk uit te voeren, elke test duurde 5 tot 8 minuten. De intra-beoordelaar betrouwbaarheid was goed voor de hamstrings, soleus en gastrocnemius (ROM: SEM range 2.9° - 5.1°, spasticiteitschaal: AA 70% - 95%, AOC: SEM 4.8° - 6.4°). Voor de adductoren, maar niet voor de rectus femoris, was de intra-beoordelaar betrouwbaarheid wel goed wanneer de spasticiteitschaal vereenvoudigd werd naar een 2-punts schaal (0,1). Op deze eenvoudige schaal wordt het wel of niet optreden van een catch gescoord. De inter-beoordelaar betrouwbaarheid was alleen goed voor de gastrocnemius (ROM: SEM 4.0°, spasticiteitschaal: AA 65%, AOC: SEM 3.6°). Deze resultaten geven aan dat herhaalde SPAT metingen altijd uitgevoerd moeten worden door één (getrainde) uitvoerder. Concluderend: mits uitgevoerd door één uitvoerder, is de SPAT een gemakkelijk uitvoerbaar en betrouwbaar klinisch meetinstrument om spasticiteit te meten in alle bestudeerde beenspieren, behalve de rectus femoris. Om de inter-beoordelaar betrouwbaarheid te verbeteren, stellen we voor dat er een speciaal trainingsprogramma moet worden ontwikkeld voor uitvoerders, en dat de snelheid waarmee de spier wordt gerekt verder gestandaardiseerd moet worden door middel van meetapparatuur.

Hoofdstuk 4 en 5 beschrijven de resultaten van een multicenter, gerandomiseerde studie naar het effect van multilevel BTX-A injecties en

intensieve revalidatie bij kinderen met CP die lopen in het flexie-patroon. Zesenvestig kinderen zijn geïnccludeerd in deze studie. De inclusie criteria waren: diagnose CP; zelfstandige loopvaardigheid (met of zonder loophulpmiddel en/of orthese); looppatroon gekenmerkt door persisterende flexie in de knie tijdens de midstance; leeftijd tussen 4 en 12 jaar oud; spasticiteit in twee of meer beenspieren, welke de mobiliteit beperkt en waarvoor multilevel BTX/A behandeling geïndiceerd is. De kinderen werden gerandomiseerd naar een interventie of controle groep. De interventiegroep werd behandeld met multilevel BTX-A injecties en intensieve revalidatie. De intensieve revalidatie bestond uit een periode van 12 weken intensieve fysiotherapie volgens een standaard protocol, ortheses, en -indien nodig (d.w.z. wanneer de ROM van de gastrocnemius minder dan 0° dorsaalflexie haalt)-, een periode van redressiegips behandeling. Kinderen in de interventiegroep werden twee keer gemeten tijdens een 6-weken durende baseline periode. Vervolgens waren er nog 4 follow-up metingen op 6, 12, 24 en 48 weken na de injecties. De kinderen in de controle groep ontvingen voor een periode van 18 tot 30 weken dezelfde behandeling zoals ze dat op dat moment gewend waren ('usual care'). Deze bestond uit lage intensiteit fysiotherapie. Sommige kinderen droegen ortheses. De kinderen in de controle groep werden tijdens deze periode elke 6 weken gemeten. Na deze baseline periode, werden ook deze kinderen behandeld met multilevel BTX-A en intensieve revalidatie, en vervolgens gemeten tijdens follow-up op 6, 12, 24 en 48 weken na injecties.

In hoofdstuk 4 worden eerst de effecten van multilevel BTX-A injecties en intensieve revalidatie vergeleken met usual care, geëvalueerd op looppatroon, spierlengte en spasticiteit. Hiervoor is het effect van de interventie groep (n=23) tot 24 weken na injectie vergeleken met het effect van usual care in de controle groep (n=23).

Het looppatroon werd beoordeeld met de Edinburgh Visual Gait Analysis Interval Testing (GAIT) schaal. Tevens werden de knie hoek tijdens midstance, de

enkel hoek tijdens midstance, de knie hoek tijdens terminal stance, en heup rotatie tijdens terminal swing gemeten. Spierlengte en spasticiteit werden gemeten met twee elementen van de SPAT, respectievelijk de ROM tijdens een langzame passieve rek (> 3 seconden) en de angle of the catch (AOC) tijdens een snelle passieve rek (< 1 seconde).

Na 6 weken was er een significante verbetering in de kwaliteit van het looppatroon (1.7 punten toename op de GAIT score, $p < 0.01$), en in de kinematica tijdens de midstance (7° verbetering naar knie extensie, $p < 0.01$) en terminal swing (5° verbetering naar knie extensie, $p < 0.01$, en 4° verbetering van de heup rotatie, $p = 0.02$). Vooral de 7° verbetering naar knie extensie in de midstance werd klinisch relevant geacht. Er werd geen effect gevonden in het looppatroon op 24 weken na injectie. Het is mogelijk dat dit tweede tijdstip te laat gekozen was om een blijvende verbetering aan te tonen, daar er geen loopanalyse was afgenomen op 12 weken. Op spierlengte werd een significante verbetering aangetoond op 6 weken na injectie in de hamstrings (9° , $p < 0.01$) en in de gastrocnemius (5° , $p < 0.01$). In beide spieren hield het effect aan tot 24 weken na injectie. Deze verbeteringen werden klinisch relevant geacht. De spierlengte van de rectus femoris en adductoren veranderde niet, maar omdat deze al op normale lengte waren voor injectie, werd een verandering hierin ook niet verwacht. Op 6 en 12 weken na injectie was de spasticiteit in de geïnjecteerde hamstrings en gastrocnemius afgenomen (resp. 11° en 6° , $p < 0.01$). Volgens de farmacologische werking van de BTX-A was dit te verwachten, aangezien bekend is dat het effect slechts tijdelijk aanhoudt. Er werd ook een significant effect gevonden in de niet-geïnjecteerde soleus (5° , $p = 0.02$). Dit zou verklaard kunnen worden door het optreden van diffusie van BTX-A van de geïnjecteerde gastrocnemius.

Uit de resultaten van deze studie werd geconcludeerd dat multilevel BTX-A en intensieve revalidatie (in vergelijking met usual care) effectief is in het verbeteren van het looppatroon, het verbeteren van de spierlengte in verkorte spieren, en het

verbeteren van de spasticiteit in met BTX-A geïnjecteerde beenspieren in kinderen met CP die lopen met knie-flexie. Alleen het effect op spierlengte was blijvend tot 24 weken na de injectie.

In Hoofdstuk 5 is de effectiviteit van multilevel BTX-A injecties en intensieve revalidatie geëvalueerd op de mobiliteit. Hiervoor is eerst het effect van de interventiegroep (n=23) tot 24 weken na injectie vergeleken met het effect van usual care in de controlegroep (n=23) in de *'trial analyse'*. Vervolgens is het lange termijn effect van de hele groep (n=46) op 48 weken na injectie geëvalueerd in de *'voor-na-analyse'*. Ten slotte zijn er *'sub-groep analyses'* uitgevoerd voor het niveau van functioneren volgens de Gross Motor Function Classification System (GMFCS) en voor leeftijd om eventuele verschillen in behandel-effect tussen deze groepen op te sporen.

De primaire uitkomstmaat voor mobiliteit was de Gross Motor Function Measure-66 (GMFM66). De secundaire uitkomstmaat was het energieverbruik tijdens het lopen (gemeten in een sub-groep van 21 kinderen) en een door ouders ingevulde probleem score (0-10 schaal).

De trial analyses toonden een significant behandel-effect in het voordeel van de interventiegroep op mobiliteit (GMFM66) op 12 en 24 weken na injectie (resp. 2.1, $p=0.02$ en 3.5 punten, $p < 0.01$). Eenzelfde effect werd gevonden op de probleemscore (resp. -1.8 en -1.7 punten, $p < 0.01$). De effecten op beide uitkomstmaten werden klinisch relevant geacht. Er werd geen effect gevonden op het energieverbruik tijdens lopen. De voor-na-analyses lieten op de GMFM66 en probleemscore ook een lange-termijn verbetering zien (resp. 2.3, $p < 0.01$; en -1.4 punten, $p < 0.01$). Ook op energieverbruik tijdens lopen werd een significante verbetering gezien (-1.8 J/kg/m, $p < 0.01$). Deze lange-termijn verbeteringen moeten echter bevestigd worden in een gerandomiseerde studie. Wat betreft het effect op het energieverbruik tijdens lopen, werd aangetoond dat kinderen die lopen met een loophulpmiddel (GMFCS niveau III) significant meer verbeteren dan

kinderen die lopen zonder loophulpmiddel (GMFCS niveaus I en II). Een mogelijke verklaring hiervoor is dat de kinderen uit de laatste groep (GMFCS niveaus I en II) niet responsief zijn voor veranderingen in hun energieverbruik, aangezien hun energieverbruik al laag is, ondanks dat het nog steeds hoger is dan dat van gezonde kinderen.

Uit de resultaten van deze studie werd geconcludeerd dat multilevel BTX-A en intensieve revalidatie (in vergelijking met usual care) een effectieve behandelmethode is in kinderen met CP die lopen met knie-flexie. Het leidt tot klinisch relevante verbeteringen in de mobiliteit, zoals aangetoond op de GMFM66 en de door ouders ervaren problemen in mobiliteit. Echter, het heeft geen effect op het energieverbruik tijdens lopen.

Kinderen met spastische CP zijn erg heterogeen met betrekking tot de ernst van hun spierfunctiestoornissen, lokalisatie van de motorische beperking, en de ernst van de aandoening op het motorisch functioneren. Het lijkt daarom aannemelijk dat bepaalde patiënten beter zullen reageren op multilevel BTX-A injecties en intensieve revalidatie dan andere. In **Hoofdstuk 6** wordt een studie beschreven waarin een poging is gedaan om predictoren te identificeren die een gunstig resultaat voorspellen van behandeling met multilevel BTX-A injecties en intensieve revalidatie bij kinderen die lopen met een flexie-patroon op het grof motorisch functioneren (gemeten met de Gross Motor Function Measure [GMFM-66]) en het looppatroon (gemeten met de knie hoek tijdens de midstance). Voor deze studie zijn de follow-up data (6, 12, 24 en 48 weken na injectie) gebruikt van de kinderen (n=46) die deelnamen aan de in de hoofdstukken 4 en 5 beschreven gerandomiseerde studie. In de literatuur zijn de volgende factoren beschreven, welke voorspellend zouden zijn voor een gunstig effect: leeftijd, geslacht, ernst van de aandoening op motorisch functioneren, lokalisatie van de motorische beperking, spierkracht, ROM, spasticiteit en gangbeeld parameters.

Van al deze factoren werden alleen leeftijd en enkel hoek tijdens de midstance voorspellend gevonden voor een verbetering in respectievelijk het grof motorisch functioneren en looppatroon. Leeftijd was dusdanig geassocieerd met het grof motorisch functioneren, dat oudere kinderen op middellange termijn (12 weken) beter reageerden op de behandeling dan jonge kinderen: dit klinisch relevante effect op de GMFM66 nam met 0.4 punten toe voor elk jaar dat het kind ouder is (op voorwaarde dat alle overige factoren gelijk blijven). De enkel hoek tijdens de midstance was dusdanig geassocieerd met het looppatroon dat het grootste lange termijn (48 weken) effect gevonden werd bij kinderen met meer enkel dorsaalflexie: per 1° toename in enkel dorsaalflexie neemt de knie hoek met 0.21° toename naar extensie. Ondanks dat deze relatie statistisch significant was, werd dit niet klinisch relevant geacht. Verder werd geconcludeerd dat de voorspellende power van de verschillende modellen zwak was; slecht 20%-40% van de totale variantie werd ermee verklaard. Benadrukt werd dat geen van de andere potentiële predictoren, geslacht, ernst aandoening op motorisch functioneren, lokalisatie van de motorische beperking, ROM en spasticiteit, op geen van de follow-up momenten voorspellend waren gevonden op de twee uitkomstmaten. Op basis van deze resultaten is leeftijd in deze patiëntengroep de enige significante en relevante predictor voor een gunstig effect op het grof motorisch functioneren na behandeling met multilevel BTX-A injecties en intensieve revalidatie.

De algemene discussie in **Hoofdstuk 7** bespreekt een aantal methodologische aspecten, alsook de voor- en nadelen van een aantal gekozen uitkomstmaten, en evalueert de effectiviteit van de multilevel BTX-A injecties en intensieve revalidatie. Geconcludeerd werd dat een gecombineerd pakket van multilevel BTX-A en intensieve revalidatie effectief is in het verbeteren van mobiliteit in kinderen met CP die lopen met een flexie-patroon. Met betrekken tot het klinisch meten van spasticiteit werd geconcludeerd dat de snelheidsafhankelijke toename van weerstand als reactie op passieve rek altijd gemeten moet worden door het bepalen

van de spierreactie bij twee verschillende snelheden van rek. Daarnaast worden in hoofdstuk 7 de implicaties voor de klinische praktijk besproken en worden er aanbevelingen gedaan voor toekomstig onderzoek.

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Over de auteur

Vanessa Scholtes, geboren op 26 maart 1975 in Den Haag. Na het behalen van mijn VWO diploma, begon ik in 1994 met de opleiding Gezondheidswetenschappen aan de Universiteit Maastricht. Mijn eerste wetenschappelijke stage deed ik bij het NOC*NSF in Papendal, waar ik vragenlijsten over de incidentie van sportblessures ontwikkelde en evalueerde. In 1998 startte ik tevens met de opleiding European Masters in Adapted Physical Activity (EMDAPA), aan de Katholieke Universiteit Leuven. België werd mijn tijdelijke ‘thuishaven’. De wetenschappelijke stage voor deze studie liep ik aan de Universiteit van Exeter in Groot Brittannië. Hier begon mijn eerste kennismaking met kinderen met cerebrale parese: in deze groep onderzocht ik de betrouwbaarheid van een nieuwe vragenlijst over zelf-waargenomen competentie.

In 1999 keerde ik terug naar Nederland en studeerde voor beide studies af. Hierna ging ik wonen en werken in Amsterdam. Ik begon mijn eerste baan als assistent in opleiding (aio) aan de afdeling reumatologie in het VU ziekenhuis (nu VU medisch centrum) en deed onderzoek bij volwassenen met reumatoïde artritis. Hoewel het klinische onderzoek mij heel goed lag, miste ik het werken met kinderen. Blij was ik daarom dat ik in 2001 de gelegenheid kreeg om de overstap te maken naar de afdeling revalidatiegeneeskunde van het VU medisch centrum. Hier voerde ik als junior onderzoeker met groot plezier het ‘BOLIEN’ onderzoek uit bij kinderen met cerebrale parese.

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Over de auteur

Op dit moment werk ik als post doctoraal onderzoeker op dezelfde afdeling en voer (wederom met groot enthousiasme) het 'POPEYE' onderzoek uit. Hierin onderzoek ik wat het effect van krachttraining is op het functioneren van kinderen met cerebrale parese. Van deze studie, waarvan de krachttraining in het najaar van 2007 zal starten, worden eind 2008 de resultaten verwacht.